10/754,541

Patent Office
Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003905406 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 06 October 2003.

WITNESS my hand this
Fourteenth day of January 2004

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

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DESCRIPTION

HDAC INHIBITOR

TECHNICAL FIELD

The present invention relates to a compound useful as a medicament, and to a pharmaceutical composition comprising the same.

BACKGROUND ART

Histone deacetylase (hereinafter also referred as HDAC) is known to play an essential role in the transcriptional machinery for regulating gene expression, induce histone hyperacetylation and to affect the gene expression. Therefore, it is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

WO 01/38322 discloses an inhibitor of histone deacetylase represented by the following formula:

$$Cy\text{-}L^1\text{-}Ar\text{-}Y^1\text{-}C(O)\text{-}NH\text{-}Z$$

wherein

Cy is cycloalkyl, aryl, heteroaryl or heterocyclyl, each of which is optionally substituted;

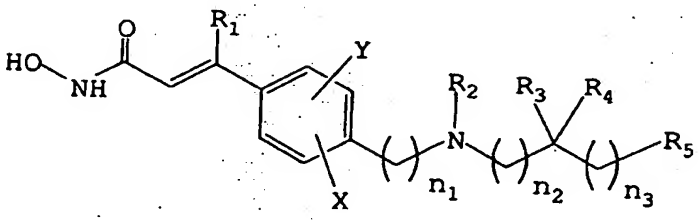
L^1 is $-(CH_2)_m-W-$ wherein m is an integer of 0 to 4, and W is selected from the group consisting of $-C(O)NH-$, $-S(O)_2NH-$, etc.;

Ar is optionally substituted arylene, which is optionally fused to an aryl, heteroaryl ring, etc.;

Y^1 is a chemical bond or a straight- or branched-chain saturated alkylene, wherein said alkylene is optionally substituted; and

Z is selected from the group consisting of anilinyl, pyridyl, thiadiazolyl and -O-M wherein M is H or a pharmaceutically acceptable cation.

WO 02/22577 discloses the following hydroxamate compound as a deacetylase inhibitor:



wherein

R_1 is H, halo or a straight chain C_1-C_6 alkyl;

R_2 is selected from H, C_1-C_{10} alkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, C_4-C_9 heterocycloalkylalkyl, cycloalkylalkyl, aryl, heteroaryl, etc.;

R_3 and R_4 are the same or different and independently H, C_1-C_6 alkyl, acyl or acylamino, or

R_3 and R_4 together with the carbon to which they are bound to represent C=O, C=S, etc., or

R_2 together with the nitrogen to which it is bound and R_3 together with the carbon to which it is bound to form a C_4-C_9 heterocycloalkyl, a heteroaryl, a polyheteroaryl, a non-aromatic polyheterocycle, or a mixed aryl and non-aryl polyheterocycle ring;

R_5 is selected from H, C_1-C_6 alkyl, etc.;

n, n_1, n_2 and n_3 are the same or different and independently selected from 0-6, when n_1 is 1-6, each carbon atom can be optionally and independently substituted with R_3 and/or R_4;

X and Y are the same or different and independently selected from H, halo, C_1-C_4 alkyl, etc.;

or a pharmaceutically acceptable salt thereof.

SUMMARY OF THE INVENTION

The present invention relates to a novel compound useful as a medicament, and to a pharmaceutical composition comprising the same.

More particularly, the present invention relates to a compound having a potent inhibitory effect on the activity of histone deacetylase.

The inventors of the present invention have also found that histone deacetylase inhibitors, such as a compound of the formula (I) (hereinafter compound [I]), have a potent immunosuppressive effect and potent antitumor effect. Therefore, a histone deacetylase inhibitors such as compound [I] is useful as an active ingredient of an immunosuppressant and an antitumor agent and useful as a therapeutic or prophylactic agent for diseases such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections, tumors, etc.

Accordingly, one object of the present invention is to provide a compound having biological activities for treating or preventing the diseases as stated above.

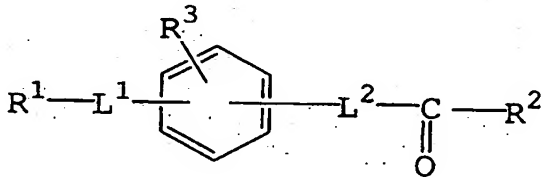
A further object of the present invention is to provide a pharmaceutical composition containing the compound [I] as an active ingredient.

A yet further object of the present invention is to provide use of the histone deacetylase inhibitors, such as compound [I], for treating and preventing the diseases as stated above.

A yet further object of the present invention is to provide a commercial package comprising the pharmaceutical composition containing the compound [I] and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing the diseases as stated above.

Thus, the present invention provides

[1] a compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

R^3 is hydrogen or a suitable substituent,

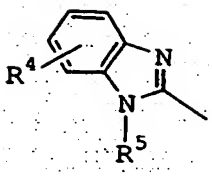
L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), wherein one or more methylene(s) may be replaced with suitable heteroatom(s), and

L^2 is lower alkenylene,

or a salt thereof;

[2] the compound of the above-mentioned [1], wherein

R^1 is N-containing condensed heterocyclic ring represented by the following formula: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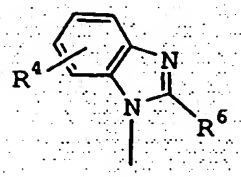
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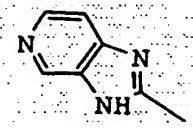
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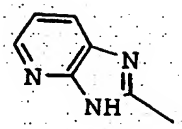
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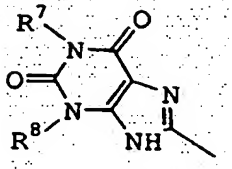
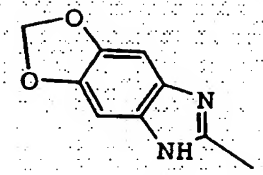

or


wherein

R^4 is hydrogen or a group selected from the group consisting of

(1) lower alkyl,

(2) lower alkoxy,

(3) aryl optionally substituted with the substituent selected from the group consisting of halogen, lower alkanoyl, lower alkylsulfonyl, lower alkoxy and di(lower)alkylamino,

(4) lower alkanoyl,

(5) lower alkoxycarbonyl,

(6) arylcarbonyl,

(7) aryl(lower)alkoxy,

(8) amino optionally mono- or di-substitited with substituent(s) selected from the group consisting of lower alkyl, lower alkanoyl and cycloalkyl,

(9) halo(lower)alkyl,

(10) aryloxy,

(11) aryl(lower)alkyl optionally substituted with hydroxy,

(12) carboxyl,

(13) nitro,

(14) cyano,

(15) halogen,

(16) heteroaryl and

(17) non-aromatic heterocycle optionally substituted with lower alkyl,

R^5 is hydrogen or a group selected from the group consisting

of lower alkyl and aryl(lower)alkyl, and

R^6, R^7 and R^8 are each hydrogen or lower alkyl,

R^2 is hydroxyamino,

R^3 is hydrogen or lower alkoxy,

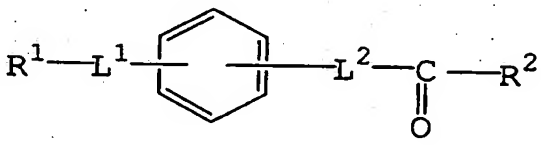
L^1 is $-(CH_2)_n-$ (wherein n is 1 or 2) optionally substituted with one or more substituent(s) selected from lower alkyl(s) and aryl(lower)alkyl, wherein two lower alkyls may form a ring, and wherein one methylene may be replaced with an oxygen atom, and

L^2 is vinylene,

or a salt thereof;

The present invention also provides another embodiment of the compound [I], which is hereinafter referred to as compound [I'].

[3] a compound of the formula (I'):



(I')

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

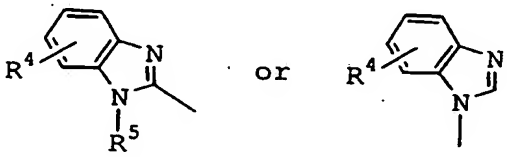
L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

or a salt thereof; and

[4] the compound of the above-mentioned [3], wherein

R^1 is N-containing condensed heterocyclic ring represented by the following formula:



wherein

R^4 is hydrogen or a group selected from the group consisting of lower alkyl and aryl, and

R^5 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl,

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is 1 or 2) optionally substituted with aryl(lower)alkyl, and

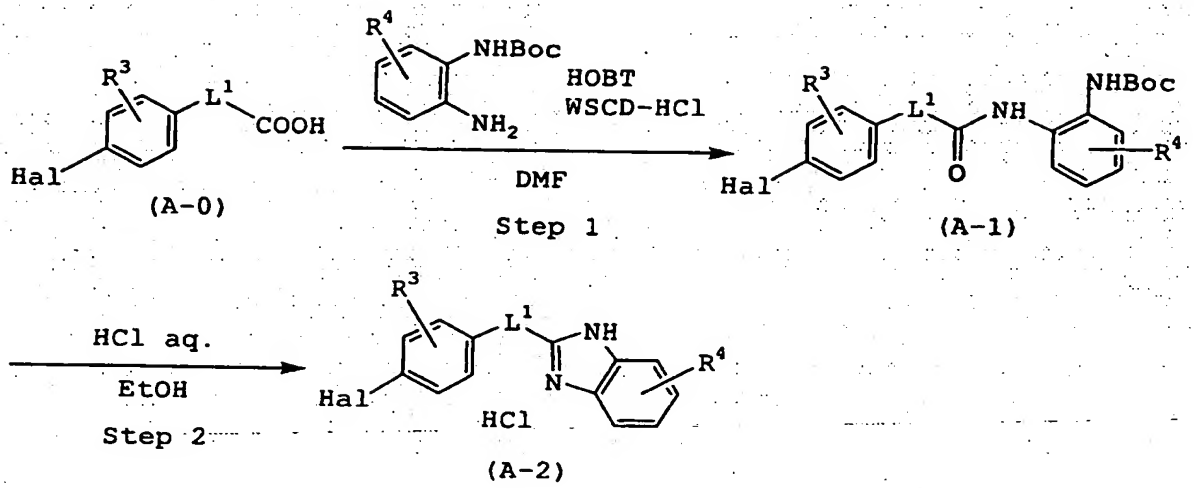
L^2 is vinylene,

or a salt thereof.

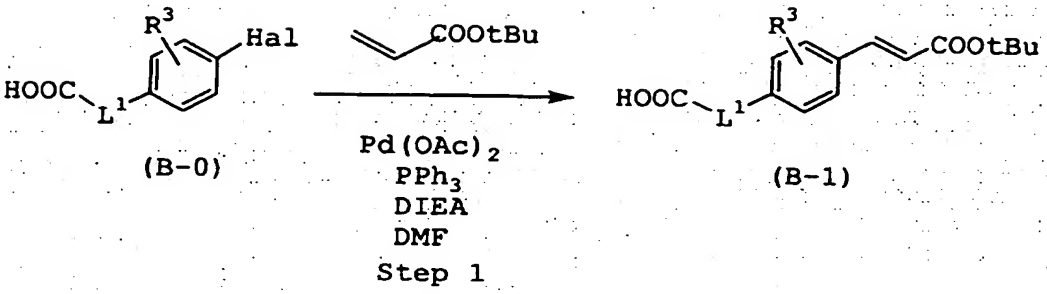
The above-mentioned compounds and salts thereof can be prepared by the processes as illustrated in the following reaction schemes.

In the following Processes, the compound [I-1] is encompassed in the scope of the compound [I], and the compound [II-A], [II-B], [II-C], [II-C'], [II-D] and [II-E] are also encompassed in the scope of the compound [II].

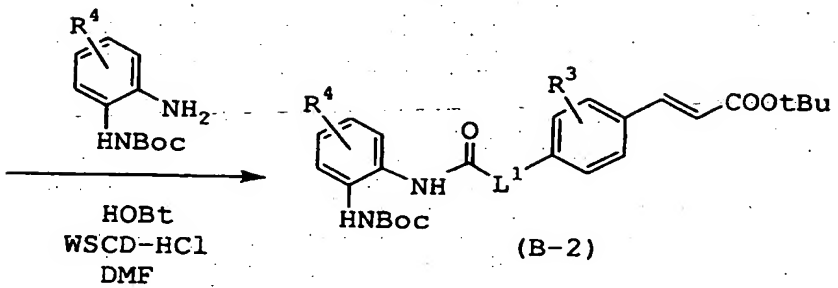
Process A


R3
L1
COOH
Hal
(A-0)
R4
NHBoc
NH2
HOBT
WSCD-HCl
DMF
Step 1
NHBoc
NH
O
R4
(A-1)
HCl aq.
EtOH
Step 2
HCl
(A-2)
1N-NaOH aq.
TsCl
dioxane
Step 3
CH3
SO2
N
(A-3)
COOH
Pd(OAc)2
(o-MePh)3P
DMF
Step 4
HOOC
(A-4)
RaO—NH2
HOBT
WSCD-HCl
DMF
Step 5
NH
ORa
[II-A]

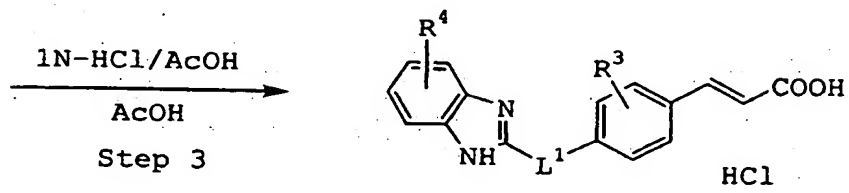
Process B



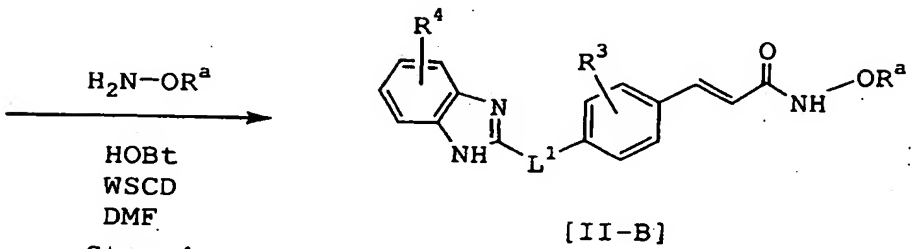
(B-0) (B-1)



(B-2)

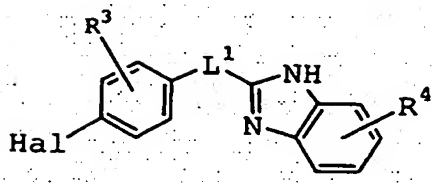


(B-3)

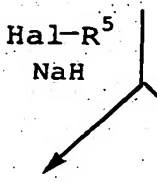


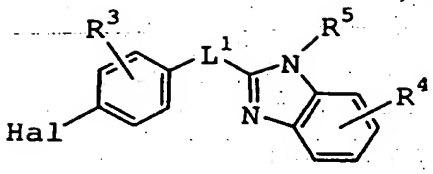
[II-B]

Process C



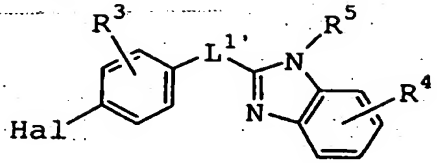
(A-2')



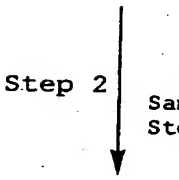


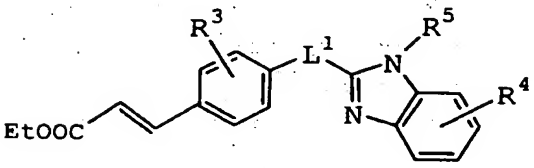
(C-1)

and



(C-1')





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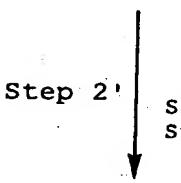
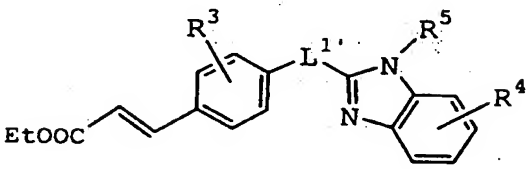
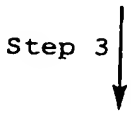
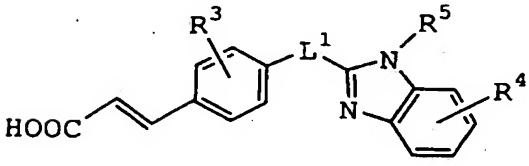


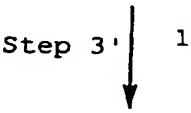


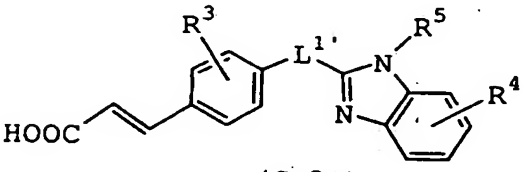
(C-2')



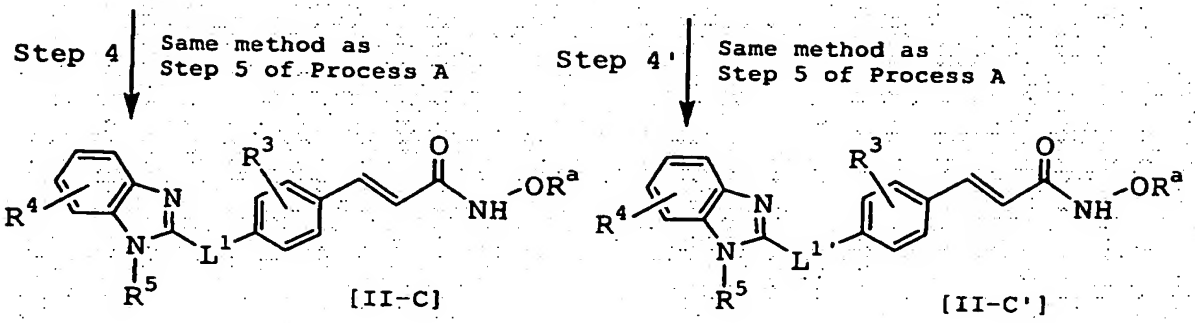


(C-3)

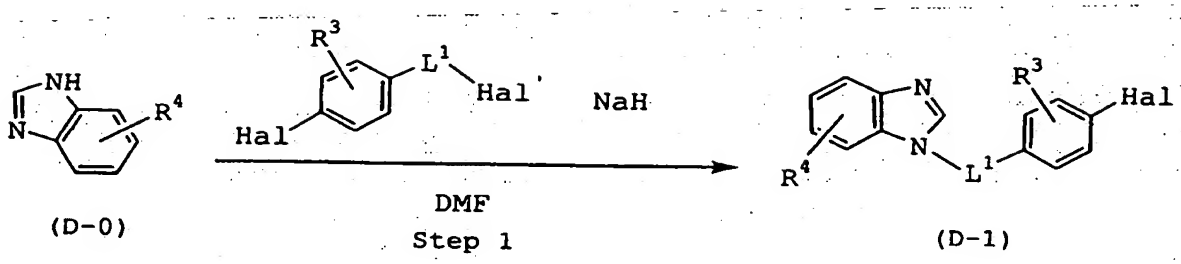


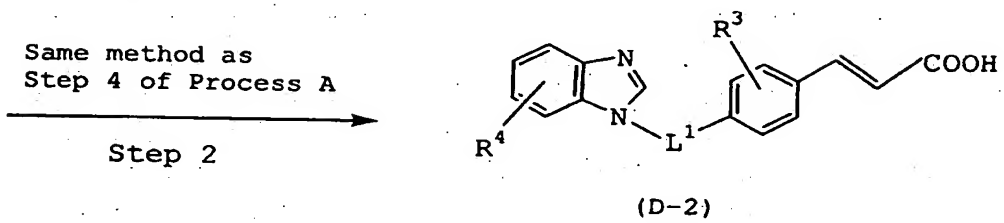


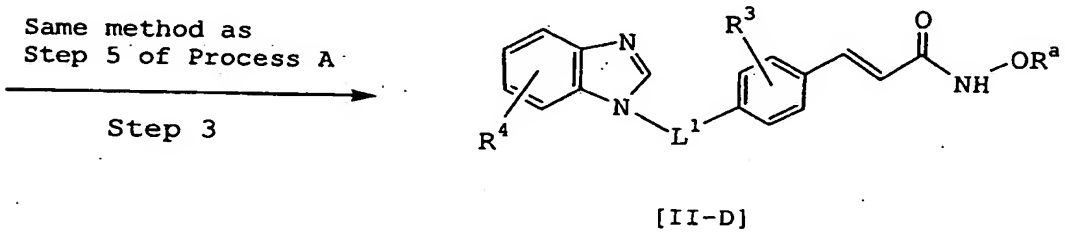
(C-3')


Step 4
Same method as
Step 5 of Process A
Step 4'
Same method as
Step 5 of Process A
[II-C]
[II-C']

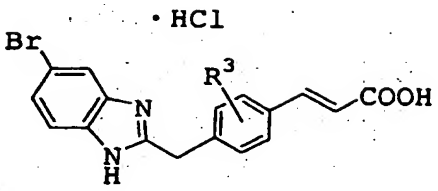
Process D


NaH
DMF
Step 1
(D-0)
(D-1)


Same method as
Step 4 of Process A
Step 2
(D-2)


Same method as
Step 5 of Process A
Step 3
[II-D]

Process E

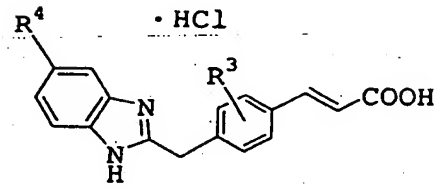


(E-0)

R^4—B(OH)$_2$

$PdCl_2(PPh_3)_2$
Na_2CO_3 aq.
dioxane

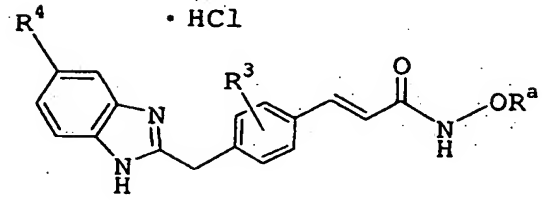
Step 1



(E-1)

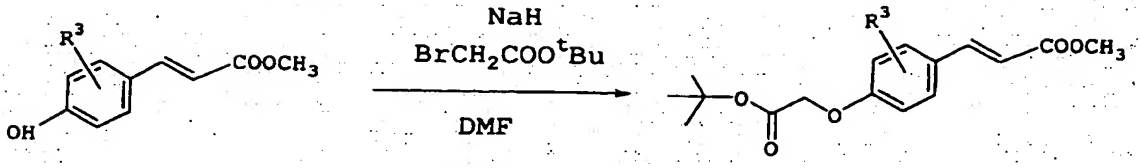
Same method as
Step 5 of Process A

Step 2

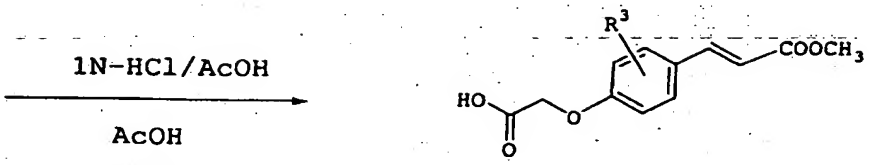


(II-E)

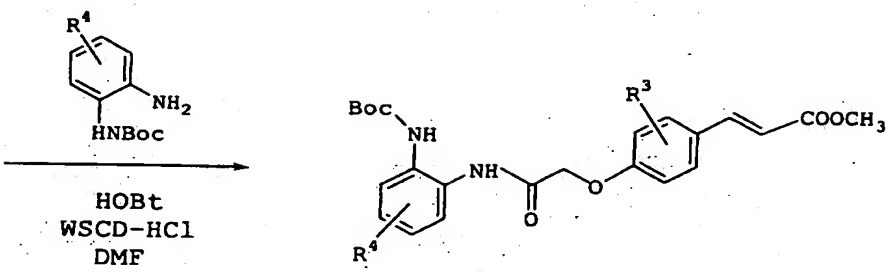
Process F



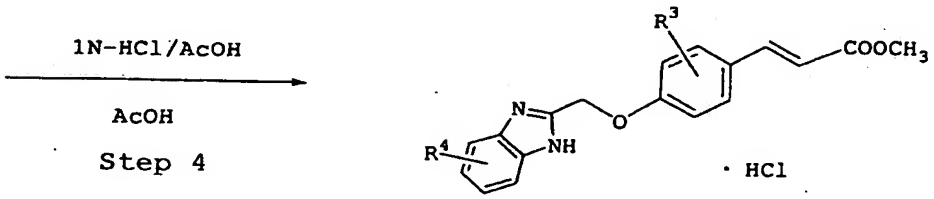
(F-0) (F-1)



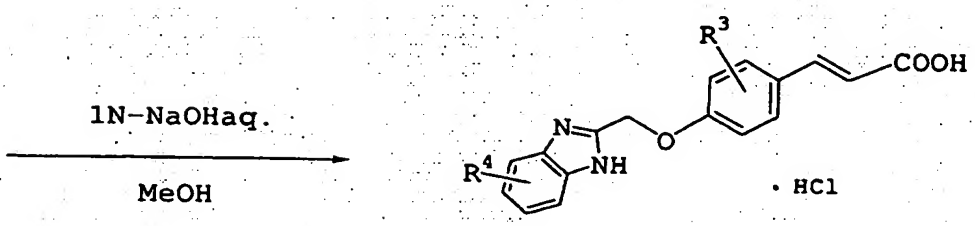
(F-2)



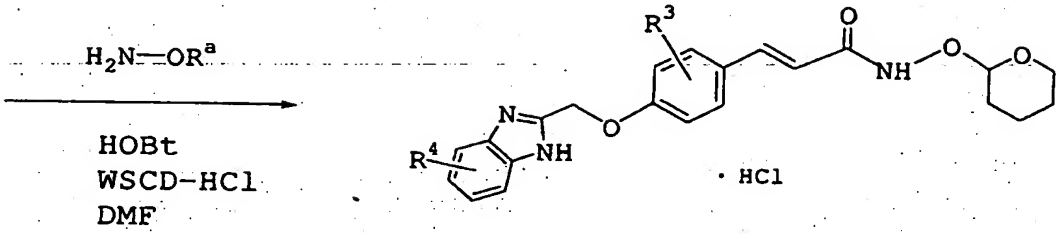
(F-3)



(F-4)



Step 5 (F-5)



Step 6 [II-F]

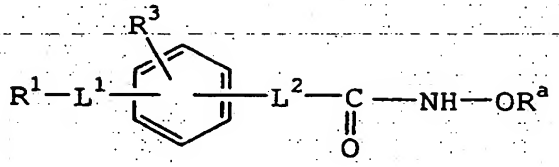
wherein R^1, R^2, R^3, R^4, R^5, L^1 and L^2 are as defined above, $L^{1'}$ is L^1 in which one of the carbon atoms is substituted with R^5 (wherein R^5 is as defined above), and R^a is a hydroxy protective group.

In the above-mentioned Processes A, B, C, D, E and F, each of the starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations in the present specification or in a manner similar thereto. For example, compounds (A-1), (A-2), (A-3) and (A-4) can be obtained by the procedures as illustrated in Preparations 1, 2, 3 and 4 respectively, compounds (B-1), (B-2) and (B-3) can be obtained by the procedures as illustrated in Preparations 6, 7 and 8 respectively, compound (C-1) and (C-1') can be obtained by the procedure as illustrated in Preparation 10, compound (C-2) and (C-3) can be obtained by the procedure as illustrated in Preparations 11 and 12 respectively, compound (C-2') and (C-3') can be obtained by the procedure as illustrated in Preparations 23 and 24 respectively, compound (D-1) and (D-2) can be obtained by the procedure as illustrated in Preparations 20 and 21 respectively, compound (E-1) can be obtained by the procedure as illustrated in Preparation 35, and compounds (F-1), (F-2), (F-3), (F-4) and (F-5)

can be obtained by the procedures as illustrated in Preparations 127, 128, 129, 130 and 131, respectively. The compounds [II-A], [II-B], [II-C], [II-C'], [II-D], [II-E] and [II-F] can be obtained, for example, by the procedure as illustrated in Preparations 5, 9, 13, 25, 22, 39 and 132, respectively.

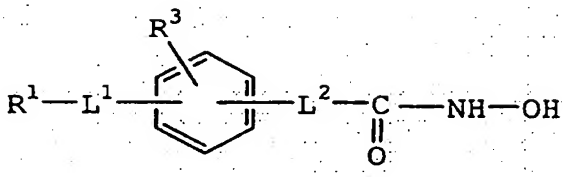
The compound [I] of the present invention is obtained from compound [II], for example, according to the following process.

Process 1



[II]

deprotection of hydroxy



[I]

wherein R^1, R^2, R^3, L^1, L^2 and R^a are as defined above.

The compound [I] is obtained by deprotecting the hydroxy group of the compound [II].

The reaction may be carried out in the presence of acid such as hydrogen chloride solution (e.g. hydrogen chloride in solvent such as methanol, dioxane, ethyl acetate, diethyl ether, etc.), acetic acid, p-toluenesulfonic acid, boric acid, etc.

Optionally, one or more suitable solvent(s) for the deprotection is(are) used. Such solvent include, for example, methanol, ethanol, ethyl acetate, dioxane, diethyl ether, acetic acid, etc.

The temperature of the reaction is not critical and the reaction is usually carried out from under cooling to heating.

This Process is exemplified by Example 1, etc.

When the compound [I] has stereoisomers, such isomers are also encompassed in the scope of the present invention.

The compound [I] may form a salt, which is also encompassed in the scope of the present invention. For example, when a basic group such as an amino group is present in a molecule, the salt is exemplified by an acid addition salt (e.g. salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc., salt with an organic acid such as methanesulfonic acid, fumaric acid, maleic acid, mandelic acid, citric acid, salicylic acid, etc.), etc., and when an acidic group such as carboxyl group is present, the salt is exemplified by a basic salt (e.g. salt with a metal such as sodium, potassium, calcium, magnesium, aluminium, etc., a salt with amino acid such as lysine, etc.), etc.

In addition, solvates of the compound [I] such as hydrate, ethanolate, etc., are also encompassed in the scope of the present invention.

Suitable examples and illustration of the various definitions in the above and subsequent descriptions, which the present invention intends to be included within the scope thereof, are explained in detail as follows:

Each of the terms "halogen", "halo" and "Hal" includes fluorine, chlorine, bromine and iodine.

The term "heteroatom" includes nitrogen atom, oxygen atom and sulfur atom.

The term "lower" used in the description is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "one or more" includes the number of 1 to 6, preferably 1 to 3.

Suitable "lower alkyl" includes straight or branched alkyl having 1 to 6 carbon atom(s) such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, neopentyl, hexyl, isohexyl, etc.

Suitable "lower alkoxy" includes straight or branched alkoxy having 1 to 6 carbon atom(s) such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy, tert-pentyloxy, neopentyloxy, hexyloxy, isohexyloxy, etc.

Suitable "lower alkanoyl" includes formyl and alkanoyl in which the alkyl portion is straight or branched alkyl having 1 to 6 carbon atom(s) such as acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, butylcarbonyl, isobutylcarbonyl, sec-

butylcarbonyl, tert-butylcarbonyl, pentylcarbonyl, tert-pentylcarbonyl, neopentylcarbonyl, hexylcarbonyl, isohexylcarbonyl, etc.

Suitable "lower alkoxycarbonyl" includes alkoxycarbonyl in which the alkyl portion is straight or branched alkyl having 1 to 6 carbon atom(s) such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, tert-pentyloxycarbonyl, neopentyloxycarbonyl, hexyloxycarbonyl, isohexyloxycarbonyl, etc.

Suitable "halo(lower)alkyl" includes lower alkyl substituted with 1 to 3 halogen atom(s) such as monochloromethyl, dichloromethyl, trichloromethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, monobromomethyl, dibromomethyl, tribromomethyl, monochloroethyl, dichloroethyl, trichloroethyl, monofluoroethyl, difluoroethyl, trifluoroethyl, etc.

Suitable "lower alkenylene" includes straight or branched alkylene having 1 to 6 carbon atom(s) such as vinylene, 1-methylvinylene, 2-methylvinylene, 1-propenylene, 2-propenylene, 2-methyl-1-propenylene, 2-methyl-2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, 1-pentenylene, 2-pentenylene, 3-pentenylene, 4-pentenylene, 1-hexenylene, 2-hexenylene, 3-hexenylene, 4-hexenylene, 5-hexenylene, etc. Suitable lower alkenylene for L^2 is, for example, vinylene, 1-methylvinylene, 2-methylvinylene, etc.

Suitable "aryl" includes C_6-C_{16} aryl such as phenyl, naphthyl, anthryl, pyrenyl, phenanthryl, azulenyl, etc.

Suitable "aryloxy" includes C_6-C_{16} aryloxy such as phenoxy, naphthyloxy, anthryloxy, pyrenyloxy, phenanthryloxy, azulenyloxy, etc.

Suitable "aryl(lower)alkyl" includes phenyl(C_1-C_6)alkyl such as benzyl, phenethyl, phenylpropyl, phenylbutyl, phenylhexyl, etc., naphthyl(C_1-C_6)alkyl such as naphthylmethyl, naphthylethyl, naphthylpropyl, naphthylbutyl, naphthylpentyl, naphtylhexyl, etc.

Suitable "arylcarbonyl" includes arylcarbonyl in which the aryl portion is C_6-C_{16} aryl such as phenylcarbonyl, naphthylcarbonyl, anthrylcarbonyl, pyrenylcarbonyl, phenanthrylcarbonyl, azulenylcarbonyl, etc.

Suitable "aryl(lower)alkoxy" includes phenyl(C_1-C_6)alkoxy such as benzyloxy, phenethyloxy, phenylpropyloxy, phenylbutyloxy, phenylhexyloxy, etc., naphthyl(C_1-C_6)alkyloxy such as naphthylmethyloxy, naphthylethyloxy, naphthylpropyloxy, naphthylbutyloxy, naphthylpentyloxy, naphtylhexyloxy, etc.

Suitable "amino" includes unsubstituted amino, and amino mono- or di-substituted with substituent(s) selected from lower alkyl, lower alkanoyl and cycloalkyl such as N-(C_1-C_6 alkyl)amino (e.g., N-methylamino, N-ethylamino, N-propylamino, N-(n-butyl)amino, N-isobutylamino, N-(t-butyl)amino, etc.), N-(C_1-C_6 alkanoyl)amino (e.g., N-acetylamino, N-ethylcarbonylamino, N-propylcarbonylamino, N-(n-butylcarbonyl)amino, N-isobutylcarbonylamino, N-(t-butylcarbonyl)amino, etc.), N-(C_3-C_6 cycloalkyl)amino (e.g., N-cyclopropylamino, N-cyclobutylamino, N-cyclopentylamino, N-cyclohexylamino, etc.), N,N-di(C_1-C_6 alkyl)amino (e.g., N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, etc.), etc.

The "heteroaryl" includes groups having 5 to 14 ring atoms and π electrons shared in a cyclic array and containing 1 to 4 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur besides carbon atoms. Suitable "heteroaryl" includes such as thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl, etc.

The "heteroaryl" and "(lower)alkyl" of the "heteroaryl(lower)alkyl" are similar to those exemplified for the "heteroaryl" and "(lower)alkyl" respectively. Suitable "heteroaryl(lower)alkyl" includes pyridylmethyl, pyridylethyl, quinolylmethyl, etc.

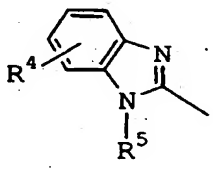
Each of the two "(lower)alkyl" of the "(lower)alkyl-carbonyl(lower)alkyl" is similar to that exemplified for the "(lower)alkyl". Suitable "(lower)alkyl-carbonyl(lower)alkyl" includes acetylmethyl, ethylcarbonylmethyl, etc.

The "non-aromatic heterocycle" includes group having 5 to 14 ring atoms and containing 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur besides carbon atoms. Suitable "non-aromatic heterocycle" includes such as pyrrolidinyl, pyrazolidinyl, imidazolidinyl, isoxazolidinyl,

isothiazolidinyl, piperidyl (e.g., piperidino etc.), piperazinyl, morpholinyl (e.g., morpholino etc.), thiomorpholinyl (e.g., thiomorpholino etc.), etc.

Suitable "N-containing condensed heterocyclic ring" for the "N-containing condensed heterocyclic ring optionally substituted with one or more substituent(s)" includes such as indolyl, isoindolyl, indolidinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, quinoxalinyl, imidazopyridyl (e.g., imidazo[4,5-c]pyridyl, etc.), tetrahydroimidazopyridyl (e.g., 4,5,6,7-tetrahydro[4,5-c]pyridyl, etc.), 7-azabicyclo[2.2.1]heptyl, 3-azabicyclo[3.2.2]nonanyl, pyridoimidazolyl (e.g. pyrido[3,2-d]imidazolyl, pyrido[4,3-d]imidazolyl, etc.), azabenzimidazolyl, etc.

Specifically, the preferred N-containing condensed heterocyclic ring optionally substituted with one or more substituent(s) represented by R^1 includes, for example, the groups represented by the following formula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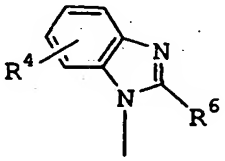
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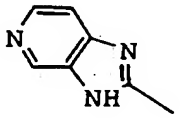
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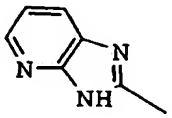
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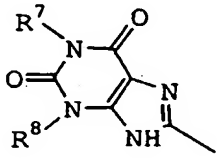
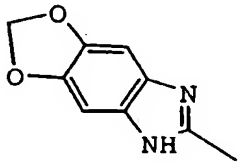

and


wherein R^4, R^5, R^6, R^7 and R^8 are as defined above.

In the above formulas, suitable substituent represented by R^4 includes such as (1) lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.); (2) lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, etc.); (3) aryl optionally substituted with the substituent selected from the group consisting of halogen, lower alkanoyl, lower alkylsulfonyl, lower alkoxy and di(lower)alkylamino (e.g., phenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-acetylphenyl, 4-(N,N-dimethylamino)phenyl, 4-fluorophenyl, 4-methylsulfonylphenyl, etc.); (4) lower alkanoyl

(e.g., acetyl, etc.); (5) lower alkoxycarbonyl (e.g., methoxycarbonyl, etc.); (6) arylcarbonyl (e.g., benzylcarbonyl, etc.); (7) aryl(lower)alkoxy (e.g., benzyloxy, etc.); (8) amino optionally mono- or di-substitited with substituent(s) selected from the group consisting of lower alkyl, lower alkanoyl and cycloalkyl (e.g., amino, N,N-dimethylamino, N,N-diethylamino, N-propylcarbonylamino, N-cyclopentylamino, etc.); (9) halo(lower)alkyl (e.g., trifluoromethyl, etc.); (10) aryloxy (e.g., phenoxy, etc.); (11) aryl(lower)alkyl optionally substituted with hydroxy (e.g., hydroxyphenylmethyl, etc.); (12) carboxyl; (13) nitro; (14) cyano; (15) halogen (e.g., fluorine, chlorine, bromine, etc.); (16) heteroaryl (e.g., thienyl, tetrazolyl, pyridyl, etc.) and (17) non-aromatic heterocycle optionally substituted with lower alkyl (e.g., 4-methylpiperadinyl, morpholino, piperidino, etc.). Furthermore, heteroaryl(lower)alkyl (e.g. pyridyl(lower)alkyl such as pyridylmethyl, etc.), lower alkyl-carbonyl(lower)alkyl (e.g. acetylmethyl, etc.), etc. can be also used for R^4.

In the above formulas, R^5 is hydrogen or a group selected from the group consisting of lower alkyl (e.g. methyl, ethyl, propyl, butyl, etc.), aryl(lower)alkyl(e.g. benzyl, phenetyl, etc.), heteroaryl(lower)alkyl (e.g. pyridyl(lower)alkyl such as pyridylmethyl, etc.) and lower alkyl-carbonyl(lower)alkyl (e.g. acetylmethyl, etc.). Preferably, R^5 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl.

In the above formulas, R^6, R^7 and R^8 are each hydrogen or lower alkyl (e.g. methyl, ethyl, propyl, butyl, etc.)

Suitable "n" of the "$-(CH_2)_n-$" for L^1 is an integer of 0 to 6, preferably 1 or 2. The "$-(CH_2)_n-$" may be optionally substituted with one or more suitable substituent(s) such as lower alkyl (e.g. methyl, ethyl, propyl, butyl, pentyl, hexyl, etc.), lower alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, etc.), aryl(lower)alkyl (e.g. benzyl, etc.), etc., wherein two substituents (e.g., two alkyls, etc.) may form a ring such as cycloalkyl ring (e.g., cyclopropyl ring, cyclobutyl ring, cyclopentyl ring, cyclohexyl ring, etc.). Furthermore, one or more methylenes (e.g., one methylene, etc.) may be replaced with suitable heteroatoms (e.g., oxygen atom, etc.).

Suitable "hydroxy protecting group" is as follows:
lower alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc., preferably methyl;
lower alkoxy(lower)alkyl (e.g. methoxymethyl, etc.);
lower alkoxy(lower)alkoxy(lower)alkyl (e.g. 2-methoxyethoxymethyl, etc.);
ar(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyl (Bn), p-methoxybenzyl, m,p-dimethoxybenzyl, etc.), preferably benzyl;
ar(lower)alkoxy(lower)alkyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxymethyl, p-methoxybenzyloxymethyl, etc.);
(lower)alkylthio(lower)alkyl (e.g. methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), etc., preferably methylthiomethyl;
trisubstituted silyl such as tri(lower)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.), lower alkyldiarylsilyl (e.g. methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl (TBDPS), etc.), etc., preferably tert-butyldimethylsilyl (TBDMS) and tert-butyldiphenylsilyl;
heterocyclic group (e.g. tetrahydropyranyl, etc.);
acyl as described below [e.g. aliphatic acyl such as lower alkanoyl (e.g. acetyl, propanoyl, pivaloyl, etc.); aromatic acyl (e.g. benzoyl (Bz), toluoyl, naphthoyl, fluorenylcarbonyl, etc.); lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.), etc.;
ar(lower)alkoxycarbonyl in which the aryl portion is optionally substituted with one or more suitable substituent(s) (e.g. benzyloxycarbonyl, bromobenzyloxycarbonyl, etc.);
lower alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.);
lower alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, etc.);
ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutanoyl, phenylpentanoyl, phenylhexanoyl,

naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, naphthylisobutanoyl, naphthylpentanoyl, naphthylhexanoyl, etc.); ar(lower)alkenoyl such as ar(C_3-C_6)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, naphthylpropenoyl, naphthylbutenoyl, naphthylmethacryloyl, naphthylpentenoyl, naphthylhexenoyl, etc.), etc.]; lower alkenyl (e.g. vinyl, allyl, etc.);, etc.

The preferable hydroxy protective group for the present invention is, for example, tetrahydropyranyl, trimethylsilyl, t-butyldimethylsilyl.

The following abbreviations are also used in the present specification: Boc (t-butyloxycarbonyl); HOBT (1-hydroxybenzotriazole); WSCD (1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide); DMF (N,N-dimethylformamide); aq. (aqueous solution); Me (methyl); MeOH (methanol); Et (ethyl); EtOH (ethanol); tBu (t-butyl); TsCl (p-toluenesulfonyl chloride); Ac (acetyl); AcOH (acetic acid); Ph (phenyl); DIEA (diisopropylethylamine); THP (tetrahydropyranyl); and TFA (trifluoroacetic acid).

Test Method

In order to show the usefulness of the compound [I] of the invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

Test 1: Determination of histone deacetylase inhibitor activity

The partial purification of human histone deacetylase, the preparation of [^{3}H] acetyl histones, and the assay for histone deacetylase activity were performed basically according to the method as proposed by Yoshida et al. as follows.

Partial purification of human histone deacetylase

The human histone deacetylase was partially purified from human T cell leukemia Jurkat cells. Jurkat cells (5 x 10^8 cells) were suspended in 40 mL of the HDA buffer consisting of 15 mM potassium phosphate, pH 7.5, 5% glycerol and 0.2 mM EDTA. After homogenization, nuclei were collected by centrifugation (35, 000 x g, 10 min) and homogenized in 20 mL of the same buffer supplemented with 1 M $(NH_4)_2SO_4$. The viscous homogenate was sonicated and clarified by centrifugation (35,000 x g, 10 min), and the deacetylase was precipitated by raising the concentration of $(NH_4)_2SO_4$ to 3.5 M. The precipitated protein was dissolved in 10 mL

of the HDA buffer and dialyzed against 4 liters of the same buffer. The dialyzate was then loaded onto a DEAE-cellulose (Whatman DE52) column (25 x 85 mm) equilibrated with the same buffer and eluted with 300 mL of a linear gradient (0-0.6 M) of NaCl. A single peak of histone deacetylase activity appeared between 0.3 and 0.4 M NaCl.

Preparation of [^{3}H] acetyl histone

To obtain [^{3}H] acetyl-labeled histone as the substrate for the histone deacetylase assay, 1 x 10^8 cells of Jurkat in 20 mL of RPMI-1640 medium (supplemented with 10% FBS, penicillin (50 units/mL) and streptomycin (50 μg/mL)) were incubated with 300 MBq [^{3}H]-sodium-acetate-in the presence of 5 mM sodium butyrate for 30 minutes in 5% CO_2-95% air atmosphere at 37°C in a 75 cm^2 flask, harvested into a centrifuge tube (50 mL), collected by centrifugation at 1000 rpm for 10 minutes, and washed once with phosphate-buffered saline. The washed cells were suspended in 15 mL of ice-cold lysis buffer (10 mM Tris-HCl, 50 mM sodium bisulfite, 1% Triton X-100, 10 mM $MgCl_2$, 8.6% sucrose, pH 6.5). After Dounce homogenization (30 stroke), the nuclei were collected by centrifugation at 1000 rpm for 10 minutes, washed 3 times with 15 mL of the lysis buffer, and once with 15 mL of ice-cooled washing buffer (10 mM Tris-HCl, 13 mM EDTA, pH 7.4) successively. The pellet was suspended in 6 mL of ice-cooled water using a mixer, and 68 μl of H_2SO_4 was added to the suspension to give a concentration of 0.4 N. After incubation at 4°C for 1 hour, the suspension was centrifuged for 5 minutes at 15, 000 rpm, and the supernatant was taken and mixed with 60 mL of acetone. After overnight incubation at -20°C, the coagulated material was collected by microcentrifugation, air-dried, and stored at -80°C.

Assay for histone deacetylase activity

For the standard assay, 10 μl of [^{3}H] acetyl-labeled histones were added to 90 μl of the enzyme fraction, and the mixture was incubated at 25°C for 30 minutes. The reaction was stopped by addition of 10 μl of HCl. The released [^{3}H] acetic acid was extracted with 1 mL of ethyl acetate, and 0.9 mL of the solvent layer was taken into 10 mL of toluene scintillation solution for determination of radioactivity.

Test 2: Determination of T-cell growth inhibitor activity

The T lymphocyte blastogenesis test was performed in

microtiter plates with each well containing 1.5×10^5 splenic cells of Lewis rats in 0.1 mL RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 mM 2-mercaptoethanol, penicilln (100 units/mL) and streptomycin (100 μg/mL), to which Concanavalin A (1 μg/mL) was added. The cells were incubated at 37°C in a humidified atmosphere of 5% CO_2 for 72 hours. After the culture period, suppressive activities of the test compounds in T lymphocyte blastogenesis were quantified by AlamarBlue (trademark) Assay. The test samples were dissolved in DMSO and further diluted with RPMI-1640 medium and added to the culture. The activities of the test compounds were expressed as IC_{50}.

The results of those tests are shown in the Table 1.

Table 1: HDAC inhibitory activity and T-cell growth inhibitory activity of the compound of the present invention

Examples	Test 1: HDAC inhibitory activity IC_{50} (nM)	Test 2: T-cell growth inhibitory activity IC_{50} (nM)
Compound E3	140	160
Compound E5	96	310
Compound E6	150	150

The pharmaceutical composition of the present invention comprising histone deacetylase inhibitor such as the compound [I] is useful as a therapeutic or prophylactic agent for diseases caused by abnormal gene expression, such as inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), protozoal infection, etc. Furthermore, it is useful as an antitumor agent or immunosuppressant, which prevents an organ transplant rejection and autoimmune diseases as exemplified below:
rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea,

myoblast, cartilage, etc.;
graft-versus-host reactions following bone marrow transplantation;
autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, etc.; and
infections caused by pathogenic microorganisms (e.g. Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, etc.).

Furthermore, pharmaceutical preparations of the histone deacetylase inhibitor, such as the compound [I], are useful for the therapy or prophylaxis of the following diseases.

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically-mediated diseases (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, alopecia areata, etc.);
autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, etc.);
reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, etc.), particularly chronic or inveterate asthma (e.g. late asthma, airway hyper-responsiveness, etc.), bronchitis, etc.];
mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases, etc.);
intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, etc.);
food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migrain, rhinitis, eczema, etc.);

renal diseases (e.g. intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, diabetic nephropathy, etc.);
nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), radiculopathy, etc.);
cerebral ischemic diseases (e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage, etc.), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy, etc.);
endocrine diseases (e.g. hyperthyroidism, Basedow's disease, etc.);
hematic diseases (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, etc.);
bone diseases (e.g. osteoporosis, etc.);
respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, idiopathic interstitial pneumonia, etc.);
skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, cutaneous T-cell lymphoma, etc.);
circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, etc.);
collagen diseases (e.g. scleroderma, Wegener's granuloma, Sjögren's syndrome, etc.);
adiposis;
eosinophilic fasciitis;
periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis, etc.);
nephrotic syndrome (e.g. glomerulonephritis, etc.);
male pattern alopecia, alopecia senile;
muscular dystrophy;
pyoderma and Sezary syndrome;
chromosome abnormality-associated diseases (e.g. Down's syndrome, etc.);
Addison's disease;
active oxygen-mediated diseases (e.g. organ injury [e.g. ischemic

circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, etc.) associated with preservation, transplantation, ischemic diseases (e.g. thrombosis, cardial infarction, etc.), etc.];
intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, drug- or radiation-induced colitis, etc.);
renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure, etc.);
pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, etc.), lung cancer, pulmonary emphysema, etc.);
ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn, etc.);
dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis, etc.); and
other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (e.g. air pollution, etc.), aging, carcinogen, metastasis of carcinoma, hypobaropathy, etc.));
diseases caused by histamine release or leukotriene C4 release;
restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;
autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g. arthritis deformans, etc.), polychondritis, etc.);
Human Immunodeficiency Virus (HIV) infection, AIDS;
allergic conjunctivitis;
hypertrophic cicatrix, keloid due to trauma, burn or surgery, etc.

Therefore, the pharmaceutical composition of the present invention is useful for the therapy and prophylaxis of liver diseases [e.g. immunogenic diseases (e.g. chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis, sclerosing cholangitis, etc.), partial liver resection,

acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock, anoxia, etc.), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, hepatic failure (e.g. fulminant hepatitis, late-onset hepatitis, "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases, etc.), etc.), etc.].

The pharmaceutical composition of the present invention can be used in the form of pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the histone deacetylase inhibitor, such as the compound [I], as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral administrations. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, injections, ointments, liniments, eye drops, lotion, gel, cream, and any other form suitable for use.

The carriers those can be used for the present invention include water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations in a solid, semisolid, or liquid form. Furthermore, auxiliary, stabilizing, thickening, solubilizing and coloring agents and perfumes may be used.

For applying the composition to human, it is preferable to apply it by intravenous, intramuscular, topical or oral administration, or by a vascular stent impregnated with the compound [I]. While the dosage of therapeutically effective amount of the histone deacetylase inhibitor, such as the compound [I], varies from and also depends upon the age and condition of each individual patient to be treated, when an individual patient is to be treated, in the case of intravenous administration, a daily dose of 0.01-10 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of human being, in the case of intramuscular administration, a daily dose of 0.1-10 mg of the histone deacetylase inhibitor, such as the compound of the formula [I], per kg weight of human being, and in the case of oral administration, a daily dose of 0.5-50 mg of the histone deacetylase inhibitor, such as the compound [I], per kg weight of

human being, is generally given for treatment.

During the preparation of the above-mentioned pharmaceutical administration forms, the compound [I] or a salt thereof can also be combined together with other immunosuppressive substances, for example repamycin, mycophenolic acid, cyclosporin A, tacrolimus or brequinar sodium.

Hereinafter the reactions in each Preparations and Examples for preparing the compound [I] of the present invention are explained in more detail. The invention should not be restricted by the following Preparations and Examples in any way.

Preparation 1

To a solution of 4-iodophenylacetic acid (1346 mg) in N,N-dimethylformamide (15 mL) was added tert-butyl 2-aminophenylcarbamate (1.07 g), 1-hydroxybenzotriazole (HOBT) (764 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (1.08 g), and the mixture was stirred at ambient temperature for 3 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was sequentially washed with saturated aqueous ammonium chloride solution, saturated aqueous sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel chromatography eluting with a mixture of hexane and ethyl acetate (4:1 to 2:1) to give Compound (1) as a pale yellow amorphous (2.03 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.50 (3x3H, s), 3.66 (2H, s), 6.62 (1H, brs), 7.07-7.20 (4H, m), 7.33 (1H, m), 7.47 (1H, m), 7.69 (2x1H, d, J=8.3 Hz), 8.00 (1H, brs);
MASS (ES+): m/e 453.

Preparation 2

To a stirred solution of Compound (1) (25.6 g) in ethanol (300 mL) was added concentrated hydrochloric acid (30 mL), and the mixture was refluxed for 1 hour. The solvent was evaporated *in vacuo* azeotropically with toluene. The residual solid was collected with the mixture of ethanol and ethyl acetate (1:10) to give Compound (2) as an orange solid (20.0 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.52 (2H, s), 7.30 (2x1H, d, J=8.3 Hz), 7.49-7.57 (2H, m), 7.73-7.82 (4H, m);
MASS (ES+): m/e 335.

Preparation 3

To a stirred solution of Compound (2) (114 mg) in dioxane (3 mL) and 1N-sodium hydroxide (0.8 mL) was added p-toluenesulfonyl chloride (70 mg) at 0°C. The mixture was allowed to warm to ambient temperature and stirred for 30 minutes. Additional p-toluenesulfonyl chloride (70 mg) was added, then 1N-sodium hydroxide (0.5 mL) was added so that the final pH was 9. The mixture was stirred at ambient temperature for 2 hours. The solvent was evaporated *in vacuo* and the resulting solution was extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography (hexane: ethyl acetate=2:1) to give Compound (3) as a pale yellow amorphous (130 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.35 (3H, s), 4.56 (2H, s), 7.05 (2x1H, d, J=8.5 Hz), 7.32-7.44 (4H, m), 7.63-7.70 (3H, m), 7.78 (2x1H, d, J=8.5 Hz), 7.94 (1H, d, J=6.5 Hz);
MASS (ES+): m/e 489.

Preparation 4

To a stirred solution of Compound (3) (1,137 mg) in N,N-dimethylformamide (15 mL) was added acrylic acid (0.8 mL), palladium(II) acetate (26 mg), tris(2-methylphenyl)phosphine (142 mg) and N,N-diisopropylethylamine (1.25 mL). The mixture was stirred at 120°C for 90 minutes. The resulting mixture was allowed to cool to ambient temperature, poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica column chromatography eluting with a mixture of chloroform and methanol (20:1) to give Compound (4) as a pale yellow amorphous (455 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.32 (3H, s), 4.63 (2H, s), 6.51 (1H, d, J=16 Hz), 7.26-7.44 (6H, m), 7.54-7.69 (4H, m), 7.79 (2x1H, d, J=8.4 Hz), 7.94 (1H, m);
MASS (ES+): m/e 433.

Preparation 5

To a stirred solution of Compound (4) (70 mg) in N,N-dimethylformamide (3 mL) was added 1-hydroxybenzotriazole (HOBT) (26 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide

hydrochloride (37 mg) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (23 mg), and the resulting mixture was stirred at ambient temperature for 14 hours. To the reaction mixture were added additional 1-hydroxybenzotriazole (13 mg), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (19 mg) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (12 mg), and the mixture was stirred for 6 hours. The reaction mixture were diluted with ethyl acetate and washed succesively with water, saturated ammonium chloride solution, saturated sodium hydrogen carbonate solution and brine. The organic phase was dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (chloroform:methanol=10:1) to give Compound (5) as a white amorphous (503 mg). The Compound (5) was used in Example 1.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.44-1.76 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 4.19 (1H, m), 4.90 (1H, m), 6.47 (1H, d, J=15.8 Hz), 7.09-7.19 (2H, m), 7.34-7.58 (7H, m), 11.23 (1H, s), 12.30 (1H, s); MASS (ES+): m/e 378.

Preparation 6

To a stirred solution of (4-bromophenyl)acetic acid (80.0 g, 372 mmol) in N,N-dimethylformamide (640 mL) was added acrylic acid t-butyl ester (95.4 g), palladium(II) acetate (1.67 g), triphenylphosphine (3.91 g) and N,N-diisopropylethylamine (162 mL). The mixture was stirred at 100°C for 7 hours. The resulting mixture was allowed to cool to ambient temperature, poured into 1N-hydrochloric acid and extracted with ethyl acetate twice. The combined organic phase was extracted with saturated sodium hydrogen carbonate solution three times. The combined aqueous phase was acidified with concentrated hydrogen chloride to pH 2 and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give Compound (6) as a pale yellow solid (78.1 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (9H, s), 3.67 (2H, s), 6.35 (1H, d, J=16 Hz), 7.29 (2H, d, J=8 Hz), 7.47 (2H, d, J=8 Hz), 7.56 (1H, d, J=16 Hz).

Preparation 7

To a solution of Compound (6) (77.7 g), tert-butyl 2-aminophenylcarbamate (61.7 g) and 1-hydroxybenzotriazole (HOBT)

(44.0 g) in N,N-dimethylformamide (777 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (62.5 g) at 4°C. The mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was added saturated aqueous sodium hydrogencarbonate (777 mL) and water (3.1 L), and extracted with ethyl acetate (1.5 L). The organic layer was washed with 5% aqueous potassium hydrogensulfate (500 mL), saturated aqueous sodium hydrogencarbonate (500 mL) and brine (500 mL), dried over magnesium sulfate, filtered and evaporated in vacuo to give Compound (7) (135 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49 (9H, s), 1.54 (9H, s), 3.74 (2H, s), 6.36 (1H, d, J=16 Hz), 6.66 (1H, brs), 7.10-7.20 (2H, m), 7.33-7.40 (3H, m), 7.44-7.54 (3H, m), 7.57 (1H, d, J=16 Hz), 7.98 (1H, brs).

Preparation 8

A solution of Compound (7) (47.6 g) in 1N-hydrogen chloride in acetic acid (60 mL) was heated at 120°C for 1 hour. The resulting mixture was allowed to cool to ambient temperature and diluted with ethyl acetate. The resulted precipitate was filtered and the residue was washed with ethyl acetate to give Compound (8) (28.9 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.56 (2H, s), 6.56 (1H, d, J=16 Hz), 7.48-7.55 (4H, m), 7.59 (1H, d, J=16 Hz), 7.72-7.80 (4H, m).

Preparation 9

To a solution of Compound (8) (50.0 g), O-tetrahydro-2H-pyran-2-ylhydroxylamine (29.8 g) and 1-hydroxybenzotriazole (34.3 g) in N,N-dimethylformamide (795 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (39.5 g) at 9°C. The mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was added saturated aqueous sodium hydrogencarbonate (795 mL) and water (3.2 L). The resulting precipitate was collected by filtation, and washed with saturated aqueous sodium hydrogencarbonate (250×2 mL) and water (250×2 mL) to give Compound (9) (57.2 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48-1.75 (6H, m), 3.48-3.57 (1H, m), 3.89-4.00 (1H, m), 4.20 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J=16 Hz), 7.07-7.16 (2H, m), 7.34-7.57 (7H, m), 11.2 (1H, brs), 12.3 (1H, brs).

Preparation 10

To a stirred solution of 2-(4-iodobenzyl)-1H-benzimidazole (451 mg) in dimethylformamide (5 ml) was added portionwise sodium hydride (81 mg, 60% oil dispersion) at 0°C. After 30 minutes, benzyl bromide (0.19 mL) was added dropwise to the mixture, and the mixture was stirred for 30 minutes. The resulting mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by preparative thin layer chromatography (chloroform:methanol=10:1) to give Compound (10) as a pale yellow oil (225 mg). In this preparation, a by-product (1-benzyl-2-[1-(4-iodophenyl)-2-phenylethyl]-1H-benzimidazole) (306 mg) was also obtained and was used in Preparation 23 described below.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.18 (2H, s), 5.19 (2H, s), 6.86-6.97 (4H, m), 7.19-7.32 (6H, m), 7.56 (2x1H, J=8.5 Hz), 7.81 (1H, d, J=7.5 Hz);

MASS (ES+): m/e 425.

Preparation 11

Compound (11) was obtained from Compound (10) according to a manner similar to Preparation 4 as a pale yellow oil (142 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7 Hz), 4.26 (2H, s), 4.26 (2H, q, J=7 Hz), 5.21 (2H, s), 6.38 (1H, d, J=16 Hz), 6.88-6.96 (2H, m), 7.18-7.32 (8H, m), 7.41 (2x1H, d, J=8 Hz), 7.62 (1H, d, J=16 Hz), 7.81 (1H, d, J=8 Hz);

MASS (ES+): m/e 397.

Preparation 12

To a stirred solution of Compound (11) (140 mg) in methanol (6 mL) was added 1N sodium hydroxide solution (0.71 mL). The mixture was stirred at ambient temperature for 7 hours. The solvent was evaporated *in vacuo*, and the residue was dissolved in water and washed with diethyl ether. The aqueous phase was acidified to pH 3 with hydrochloric acid, and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over sodium sulfate and evaporated *in vacuo* to give Compound (12) as a pale yellow powder (111 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 4.29 (2H, s), 5.23 (2H, s), 6.36 (1H, d, J=15.7 Hz), 6.88-6.96 (2H, m), 7.16-7.34 (8H, m), 7.41 (2x1H, d, J=8 Hz), 7.62 (1H, d, J=15.7 Hz), 7.81 (1H, d, J=7.5 Hz);

MASS (ES+): m/e 368.

Preparation 13

Compound (13) was obtained from Compound (12) according to a manner similar to Preparation 9 as a white amorphous (111 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.52-1.95 (6H, m), 3.61 (1H, m), 3.94 (1H, m), 4.25 (2H, s), 5.02 (1H, m), 5.20 (2H, s), 6.88-6.96 (2H, m), 7.12-7.41 (11H, m), 7.66 (1H, d, J=15.5 Hz), 7.82 (1H, d, J=8 Hz);

MASS (ES+): m/e 468.

Preparation 14

To a stirred solution of 3-phenylpropanoic acid (7.51 g) in acetic acid (70 mL) were added periodic acid (2.39 g), iodine (5.08 g), concentrated sulfuric acid (1.5 mL) and water (10 mL), and the mixture was stirred at 70°C for 7 hours. The solvent was evaporated *in vacuo*, and the residue was diluted with water and extracted with ethyl acetate. The organic phase was washed with 10% sodium thiosulfate solution twice, then washed with brine, dried over magnesium sulfate and evaporated *in vacuo*. The precipitate was crystallized from ethyl acetate and hexane to give Compound (14) (5.80 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.66 (2H, t, J=7 Hz), 2.90 (2H, t, J=7 Hz), 6.97 (2x1H, d, J=8.5 Hz), 7.61 (2x1H, d, J=8.5 Hz);

MASS (ES-): m/e 275.

Preparation 15

Compound (15) was obtained from Compound (14) according to a manner similar to Preparation 1 (9.50 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.51 (3x3H, s), 2.64 (2H, t, J=7.5 Hz), 3.00 (2H, t, J=7.5 Hz), 6.69 (1H, s), 7.00 (2x1H, d, J=8.5 Hz), 7.12-7.20 (2H, m), 7.33 (1H, m), 7.45 (1H, m), 7.62 (2x1H, d, J=8.5 Hz), 7.97 (1H, brs);

MASS (ES+): m/e 467.

Preparation 16

Compound (16) was obtained from Compound (15) according to a manner similar to Preparation 2 (1.55 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.20 (2H, t, J=7.5 Hz), 3.41 (2H, t, J=7.5 Hz), 7.10 (2x1H, d, J=8.5 Hz), 7.48-7.56 (2H, m), 7.66 (2x1H, d, J=8.5 Hz), 7.74-7.82 (2H, m);

MASS (ES+): m/e 349.

Preparation 17

Compound (17) was obtained from Compound (16) according to a manner similar to Preparation 3 (7.10 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.38 (3H, s), 3.18 (2H, t, J=7 Hz), 3.43 (2H, t, J=7 Hz), 7.05 (2x1H, d, J=8.5 Hz), 7.25 (2x1H, d, J=8.5 Hz), 7.30-7.40 (2H, m), 7.61 (2x1H, d, J=8.5 Hz), 7.67 (1H, m), 7.71 (2x1H, d, J=8.5 Hz), 8.03 (1H, m);

MASS (ES+): m/e 503.

Preparation 18

Compound (18) was obtained from Compound (17) according to a manner similar to Preparation 4 (3.59 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.38 (3H, s), 3.27 (2H, t, J=7 Hz), 3.47 (2H, t, J=7 Hz), 6.44 (1H, d, J=16 Hz), 7.25 (2x1H, d, J=8 Hz), 7.31-7.40 (4H, m), 7.50 (2x1H, d, J=8 Hz), 7.66-7.81 (4H, m), 8.04 (1H, m);

MASS (ES+): m/e 447.

Preparation 19

Compound (19) was obtained from Compound (18) according to a manner similar to Preparation 5 (2.20 g). The Compound (19) was used in Example 3.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.08-3.18 (4H, m), 3.53 (1H, m), 3.95 (1H, m), 4.90 (1H, m), 6.45 (1H, d, J=15.5 Hz), 7.08-7.16 (2H, m), 7.31 (2x1H, d, J=8 Hz), 7.40-7.54 (5H, m), 11.21 (1H, s), 12.28 (1H, br);

MASS (ES+): m/e 392.

Preparation 20

To a stirred solution of 1H-benzimidazole (500 mg) in N,N-dimethylformamide (10 mL) was added sodium hydride (186 mg, 60% of oil suspension) at 0°C. After 90 minutes, 4-iodobenzyl bromide was added to the mixture and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution, diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was triturated with hexane to give Compound (20) as a white solid. (1.20 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.31 (2H, s), 6.92 (2x1H, d, J=8.5 Hz), 7.21-7.33 (3H, m), 7.67 (2x1H, d, J=8.5 Hz), 7.84 (1H, m), 7.95 (1H,

s);

MASS (ES+): m/e 335.

Preparation 21

Compound (21) was obtained from Compound (20) according to a manner similar to Preparation 4 (614 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.53 (2H, s), 6.50 (1H, d, J=16 Hz), 7.15-7.24 (2H, m), 7.32 (2x1H, d, J=8.5 Hz), 7.51 (1H, m), 7.52 (1H, d, J=16 Hz), 7.61-7.70 (3H, m), 8.43 (1H, s);

MASS (ES+): m/e 279.

Preparation 22

Compound (22) was obtained from Compound (21) according to a manner similar to Preparation 5 (536 mg). The obtained Compound (22) was used in Example 4.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.76 (6H, m), 3.52 (1H, m), 3.94 (1H, m), 4.89 (1H, m), 5.53 (2H, s), 6.46 (1H, d, J=16 Hz), 7.16-7.25 (2H, m), 7.33 (2x1H, d, J=8.5 Hz), 7.44 (1H, d, J=16 Hz), 7.51 (1H, m), 7.54 (2x1H, d, J=8.5 Hz), 7.67 (1H, m), 8.42 (1H, s), 11.24 (1H, s);

MASS (ES+): m/e 378.

Preparation 23

Compound (23) was obtained from the by-product obtained in Preparation 10 according to a manner similar to Preparation 4 (150 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.32 (3H, t, J=7 Hz), 3.35 (1H, dd, J=13.5, 7.5 Hz), 3.85 (1H, dd, J=13.5, 7.5 Hz), 4.25 (2H, q, J=7 Hz), 4.28 (1H, dd, J=7.5, 7.5 Hz), 5.05 (1H, d, J=16.5 Hz), 5.11 (1H, d, J=16.5 Hz), 6.35 (1H, d, J=16 Hz), 6.75 (2x1H, dd, J=7.5, 1 Hz), 6.93-7.00 (2H, m), 7.09-7.38 (13H, m), 7.59 (1H, d, J=16 Hz), 7.91 (1H, d, J=8 Hz);

MASS (ES+): m/e 487.

Preparation 24

Compound (24) was obtained from Compound (23) according to a manner similar to Preparation 12 (135 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.37 (1H, dd, J=13.5, 7.5 Hz), 3.86 (1H, dd, J=13.5, 7.5 Hz), 4.31 (1H, dd, J=7.5, 7.5 Hz), 5.06 (1H, d, J=15.7 Hz), 5.11 (1H, d, J=15.7 Hz), 6.39 (1H, d, J=15.7 Hz), 6.74 (2x1H, d, J=7 Hz), 6.93-7.02 (2H, m), 7.08-7.33 (11H, m), 7.36 (2x1H, d, J=8 Hz), 7.68 (1H, d, J=15.7 Hz), 7.94 (2x1H, d, J=7.5

Hz);
MASS (ES+): m/e 459.

Preparation 25

Compound (25) was obtained from Compound (24) according to a manner similar to Preparation 9 (140 mg). The obtained Compound (25) was used in Example 5.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.55-1.92 (6H, m), 3.35 (1H, dd, J=13.5, 7.5 Hz), 3.64 (1H, m), 3.84 (1H, dd, J=13.5, 7.5 Hz), 3.95 (1H, m), 4.28 (1H, dd, J=7.5, 7.5 Hz), 5.00 (1H, m), 5.04 (1H, d, J=17 Hz), 5.11 (1H, d, J=17 Hz), 6.75 (2x1H, d, J=7 Hz), 6.92-7.00 (2H, m), 7.08-7.37 (14H, m), 7.64 (1H, d, J=15 Hz), 7.90 (1H, d, J=8 Hz);
MASS (ES+): m/e 558.

Preparation 26

Compound (26) was obtained from (3-bromophenyl)acetic acid according to a manner similar to Preparation 6 (6.20 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (3x3H, s), 3.06 (2H, s), 6.37 (1H, d, J=15.8 Hz), 7.25-7.46 (4H, m), 7.56 (1H, d, J=15.8 Hz);
MASS (ES-): m/e 261.

Preparation 27

Compound (27) was obtained from Compound (26) according to a manner similar to Preparation 7 (6.96 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.48 (3x3H, s), 1.53 (3x3H, s), 3.74 (2H, s), 6.39 (1H, d, J=15.8 Hz), 6.70 (1H, brs), 7.09-7.20 (2H, m), 7.32-7.52 (6H, m), 7.56 (1H, d, J=15.8 Hz), 8.04 (1H, brs):
MASS (ES+): m/e 453.

Preparation 28

Compound (28) was obtained from Compound (27) according to a manner similar to Preparation 8 (4.19 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.58 (1H, d, J=16 Hz), 7.42-7.58 (5H, m), 7.58 (1H, d, J=16 Hz), 7.66 (1H, m), 7.74-7.82 (2H, m), 7.87 (1H, brs);
MASS (ES+): m/e 279.

Preparation 29

Compound (29) was obtained from Compound (28) according to a manner similar to Preparation 9 (3.34 g). The obtained Compound (29) was used in Example 6.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.44-1.76 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.20 (2H, s), 4.90 (1H, m), 6.50 (1H, d, J=16 Hz), 7.08-

7.16 (2H, m), 7.32-7.60 (7H, m), 11.25 (1H, s), 12.31 (1H, brs);
MASS (ES+): m/e 378.

Preparation 30

Compound (30) was obtained from {4-[(1E)-3-tert-butoxy-3-oxo-1-propenyl]phenyl}acetic acid according to a manner similar to Preparation 1 (324 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48 (3x3H, s), 3.176 (1H, s), 3.723 (1H, s), 5.00 (1H, s), 5.01 (1H, s), 6.51 (1H, d, J=15.7 Hz), 6.82 (1H, m), 7.19-7.60 (10H, m), 7.66 (2x1H, d, J=8 Hz), 9.45 (0.5H, s), 9.47 (0.5H, s);

MASS (ES+): m/e 429.

Preparation 31

Compound (31) was obtained from Compound (30) according to a manner similar to Preparation 8 (216 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.59 (2H, s), 6.57 (1H, d, J=16 Hz), 7.42 (1H, m), 7.51 (2x1H, d, J=7.5 Hz), 7.53 (2x1H, d, J=8.5 Hz), 7.60 (1H, d, J=16 Hz), 7.69-7.88 (6H, m), 7.96 (1H, s);

MASS (ES+): m/e 355.

Preparation 32

Compound (32) was obtained from Compound (31) according to a manner similar to Preparation 9 (231 mg). The obtained Compound (32) was used in Example 7.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.78 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 4.22 (2H, s), 4.90 (1H, m), 6.48 (1H, d, J=15 Hz), 7.30-7.81 (13H, m), 11.23 (1H, s), 12.38 (1/2H, s), 12.41 (1/2H, s);

MASS (ES+): m/e 454.

Preparation 33

Compound (33) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (5.48 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.50 (2H, s), 6.55 (1H, d, J = 16 Hz), 7.47 (2H, d, J = 8 Hz), 7.59 (1H, d, J = 16 Hz), 7.56-7.75 (4H, m), 7.97 (1H, s).

MASS (ESI): m/z 357 (M+1).

Preparation 34

Compound (34) was obtained from Compound (33) according to a manner similar to Preparation 9 (557 mg). The Compound (34) was used in Example 8.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48-1.74 (6H, m), 3.48-3.57 (1H, m),

3.89-4.00 (1H, m), 4.20 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.26 (1H, dd, J = 2, 8 Hz), 7.34-7.56 (6H, m), 7.68 (1H, brs).

MASS (ESI): m/z 456 (M+1).

Preparation 35

To a mixture of Compound (34) (200 mg), 4-acetylphenylboronic acid (167 mg) and dichlorobis(triphenylphosphine)palladium(II) (10.7 mg) in dioxane (10 mL) was added 2M sodium carbonate (2.5 mL), and the mixture was heated at 90°C for 5 hours. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The inorganic layer was separated and acidified with 1N hydrochloric acid. The resulting precipitate was collected by filtration, and washed with water and ethyl acetate to give Compound (35) (193 mg). The Compound (35) was used in Example 9.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.63 (3H, s), 4.57 (2H, s), 6.56 (1H, d, J = 16 Hz), 7.52 (2H, d, J = 8 Hz), 7.59 (1H, d, J = 16 Hz), 7.74 (2H, d, J = 8 Hz), 7.85-7.92 (4H, m), 8.03-8.10 (3H, m);

MASS (ESI): m/z 397 (M+1).

Preparation 36

Compound (36) was obtained from Compound (34) according to a manner similar to Preparation 35 (163 mg). The Compound (36) was used in Example 10.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.37 (2H, s), 6.53 (1H, d, J = 16 Hz), 7.12-7.16 (1H, m), 7.45-7.71 (9H, m), 7.81 (1H, s);

MASS (ESI): m/z 361 (M+1).

Preparation 37

Compound (37) was obtained from Compound (34) according to a manner similar to Preparation 35 (183 mg). The Compound (37) was used in Example 11.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.55 (2H, s), 6.56 (1H, d, J = 16 Hz), 7.40-8.01 (11H, m);

MASS (ESI): m/z 361 (M+1).

Preparation 38

Compound (38) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (2.07 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.47 (2H, s), 6.54 (1H, d, J = 16 Hz), 7.46 (2H, d, J = 8 Hz), 7.58 (1H, d, J = 16 Hz), 7.70 (2H, d, J = 8

Hz), 7.77 (1H, d, J = 8 Hz), 7.83 (1H, d, J = 8 Hz), 8.26 (1H, s);
MASS (ESI): m/z 304 (M+1).

Preparation 39

Compound (39) was obtained from Compound (38) according to a manner similar to Preparation 9 (2.14 g). The Compound (39) was used in Examples 12 and 18.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.49-1.72 (6H, m), 3.50-3.56 (1H, m), 3.91-3.99 (1H, m), 4.26 (2H, s), 4.91 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.37 (2H, d, J = 8 Hz), 7.46 (1H, d, J = 16 Hz), 7.51-7.57 (3H, m), 7.65 (1H, d, J = 8 Hz), 8.32 (1H, brs);
MASS (ESI): m/z 401 (M-1).

Preparation 40

Compound (40) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (955 mg). The Compound (40) was used in Example 13.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.50 (2H, s), 6.55 (1H, d, J = 16 Hz), 7.32-7.39 (1H, m), 7.47 (2H, d, J = 8 Hz), 7.59 (1H, d, J = 16 Hz), 7.62 (1H, dd, J = 2, 8 Hz), 7.72 (2H, d, J = 8 Hz), 7.74-7.79 (1H, m);
MASS (ESI): m/z 297 (M+1).

Preparation 41

Compound (41) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (1.02 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.52 (2H, s), 6.55 (1H, d, J = 16 Hz), 7.48 (2H, d, J = 8 Hz), 7.50 (1H, dd, J = 2, 8 Hz), 7.59 (1H, d, J = 16 Hz), 7.72 (2H, d, J = 8 Hz), 7.75 (1H, d, J = 8 Hz), 7.85 (1H, J = 2 Hz);
MASS (ESI): m/z 313 (M+1).

Preparation 42

Compound (42) was obtained from Compound (41) according to a manner similar to Preparation 9 (839 mg). The Compound (42) was used in Example 14.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.49-1.71 (6H, m), 3.49-3.57 (1H, m), 3.88-4.02 (1H, m), 4.20 (2H, s), 4.88-4.93 (1H, m), 6.43-6.52 (1H, m), 7.12-7.18 (1H, m), 7.36 (2H, d, J = 8 Hz), 7.46 (1H, d, J = 16 Hz), 7.53 (2H, d, J = 8 Hz), 7.53-7.60 (1H, m), 7.64 (1H, d, J = 8 Hz);
MASS (ESI): m/z 412 (M+1).

Preparation 43

Compound (43) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (411 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.78-2.84 (4H, m), 3.13-3.20 (4H, m), 4.54 (2H, s), 6.55 (1H, d, J = 16 Hz), 7.16-7.76 (8H, m);

MASS (ESI): m/z 377 (M+1).

Preparation 44

Compound (44) was obtained from Compound (43) according to a manner similar to Preparation 9 (23 mg). The Compound (44) was used in Example 15.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.54-1.87 (6H, m), 2.36 (3H, s), 2.58-2.64 (4H, m), 3.12-3.20 (4H, m), 3.58-3.66 (1H, m), 3.92-4.04 (1H, m), 4.15 (2H, s), 5.02-5.10 (1H, m), 6.92-7.60 (9H, m);

MASS (ESI): m/z 476 (M+1).

Preparation 45

Compound (45) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (358 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.16-3.22 (4H, m), 3.76-3.83 (4H, m), 4.53 (2H, s), 6.56 (1H, d, J = 16 Hz), 7.34-7.76 (8H, m);

MASS (ESI): m/z 364 (M+1).

Preparation 46

Compound (46) was obtained from Compound (45) according to a manner similar to Preparation 9 (59 mg). The Compound (46) was used in Example 16.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.51-1.87 (6H, m), 3.05-3.13 (4H, m), 3.57-3.64 (1H, m), 3.83-3.91 (4H, m), 3.95-4.04 (1H, m), 4.15 (2H, s), 5.04-5.13 (1H, m), 6.91-7.61 (9H, m);

MASS (ESI) : m/z 463 (M+1).

Preparation 47

Compound (47) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (517 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.57-1.69 (2H, m), 1.83-1.94 (4H, m), 3.37-3.50 (4H, m), 4.52 (2H, s), 6.48-6.58 (1H, m), 7.40-7.74 (8H, m);

MASS (ESI): m/z 362 (M+1).

Preparation 48

Compound (48) was obtained from Compound (47) according to a manner similar to Preparation 9 (47 mg). The Compound (48) was

used in Example 17.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.50-1.87 (12H, m), 3.05-3.11 (4H, m), 3.57-3.66 (1H, m), 3.94-4.05 (1H, m), 4.14 (2H, s), 5.02-5.12 (1H, m), 6.94-7.48 (9H, m);

MASS (ESI): m/z 461 (M+1).

Preparation 49

Compound (49) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (1.17 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.90 (3H, s), 4.49 (2H, s), 6.54 (1H, d, J = 16 Hz), 7.47 (2H, d, J = 8 Hz), 7.59 (1H, d, J = 16 Hz), 7.72 (2H, d, J = 8 Hz), 7.78 (1H, d, J = 8 Hz), 8.00 (1H, dd, J = 2, 8 Hz), 8.24 (1H, brs);

MASS (ESI) : m/z 337 (M+1).

Preparation 50

Compound (50) was obtained from Compound (49) according to a manner similar to Preparation 9 (1.30 g). The Compound (50) was used in Example 19.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48-1.74 (6H, m), 3.48-3.58 (1H, m), 3.85 (3H, s), 3.87-4.00 (1H, m), 4.25 (2H, brs), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.35-7.65 (6H, m), 7.74-8.16 (2H, m);

MASS (ESI): m/z 436 (M+1).

Preparation 51

To a solution of Compound (50) (299 mg) in dioxane (7 mL) was added 1N sodium hydroxide (2.1 mL). After stirring at 80°C for 1 hour, the reaction mixture was added water (25 mL) and acidified with 1N hydrochloric acid (to pH 3-4). A resulting precipitate was collected by filtration and washed with water to give Compound (51) (255 mg). The Compound (51) was used in Example 20.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.49-1.74 (6H, m), 3.47-3.59 (1H, m), 3.87-4.01 (1H, m), 4.24 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.38 (2H, d, J = 8 Hz), 7.43-7.62 (4H, m), 7.73-8.14 (2H, m);

MASS (ESI): m/z 422 (M+1).

Preparation 52

Compound (52) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (384 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.68 (3H, s), 4.55 (2H, s), 6.55 (1H, d, J = 16 Hz), 7.50 (2H, d, J = 8 Hz), 7.59 (1H, d, J = 16 Hz),

7.73 (2H, d, J = 8 Hz), 7.81 (1H, d, J = 8 Hz), 8.04 (1H, dd, J = 2, 8 Hz), 8.27 (1H, s);
MASS (ESI): m/z 321 (M+1).

Preparation 53

Compound (53) was obtained from Compound (52) according to a manner similar to Preparation 9 (394 mg). The Compound (53) was used in Example 21.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.47-1.73 (6H, m), 2.61 (3H, s), 3.48-3.57 (1H, m), 3.90-4.01 (1H, m), 4.25 (2H, brs), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.36-8.23 (8H, m);
MASS (ESI): m/z 418 (M-1).

Preparation 54

Compound (54) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (335 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.53 (1H, d, J = 16 Hz), 7.30-7.36 (1H, m), 7.47 (2H, d, J = 8 Hz), 7.54-7.73 (5H, m);
MASS (ESI): m/z 357 (M+1).

Preparation 55

Compound (55) was obtained from Compound (54) according to a manner similar to Preparation 9 (364 mg). The Compound (55) was used in Example 22.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48-1.74 (6H, m), 3.48-3.58 (1H, m), 3.89-4.02 (1H, m), 4.24 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.05-7.12 (1H, m), 7.33-7.58 (7H, m);
MASS (ESI): m/z 456 (M+1).

Preparation 56

Compound (56) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (805 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.24 (3H, s), 1.27 (3H, s), 3.02-3.15 (1H, m), 4.54 (2H, s), 6.56 (1H, d, J = 16 Hz), 7.33-7.75 (8H, m);
MASS (ESI): m/z 321 (M+1).

Preparation 57

Compound (57) was obtained from Compound (56) according to a manner similar to Preparation 9 (70 mg). The Compound (57) was used in Example 23.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.22 (3H, s), 1.24 (3H, s), 1.48-1.73 (6H, m), 2.89-3.03 (1H, m), 3.48-3.57 (1H, m), 3.89-4.00 (1H, m), 4.17 (2H, s), 4.90 (1H, brs), 6.47 (1H, d, J = 16 Hz), 7.01 (1H, d,

J = 8 Hz), 7.20-7.57 (7H, m);
MASS (ESI): m/z 420 (M+1).

Preparation 58

Compound (58) was obtained from Compound (6) according to manners similar to Preparations 7 and 8 (925 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.50 (2H, s), 5.37 (2H, s), 6.54 (1H, d, J = 16 Hz), 7.13-7.75 (13H, m);
MASS (ESI): m/z 385 (M+1).

Preparation 59

Compound (59) was obtained from Compound (58) according to a manner similar to Preparation 9. The Compound (59) was used in Example 24.

Preparation 60

Compound (60) was obtained according to a manner similar to Preparation 20 (1.25 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.56 (3H, s), 5.27 (2H, s),6 .79 (2x1H, d, J=8.4 Hz), 7.15-7.29 (3H, m), 7.63 (2x1H, d, J=8.4 Hz), 7.73 (1H, m);
MASS (ES+): m/e 349.

Preparation 61

Compound (61) was obtained from Compound (60) according to a manner similar to Preparation 4 (625 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.57 (3H, s), 5.36 (2H, s), 6.40 (1H, d, J=16.2 Hz), 7.07 (2x1H, d, J=8.5 Hz), 7.20-7.29 (3H, m), 7.48 (2x1H, d, J=8.5 Hz), 7.64 (1H, d, J=16.2 Hz), 7.71 (1H, m);
MASS (ES+): m/e 293.

Preparation 62

Compound (62) was obtained from Compound (61) according to a manner similar to Preparation 9 (556 mg). The Compound (62) was used in Example 25.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.75 (6H, m), 2.52 (3H, s), 3.52 (1H, m), 3.94 (1H, m), 4.89 (1H, m), 5.50 (2H, s), 6.46 (1H, d, J=16 Hz), 7.11-7.20 (4H, m), 7.38-7.62 (5H, m);
MASS (ES+): m/e 392.

Preparation 63

To a stirred solution of 1-phenylcyclopropanecarboxylic acid (3.25 g) in acetic acid (30 mL) was added periodic acid (959 mg), iodine (2.03 g), concentrated H_2SO_4 (0.6 mL) and water (4 mL), and

the mixture was stirred at 70°C for 12 hours. Water (100 mL) was added to the mixture and the precipitated solid was collected by filtration and washed with water to give Compound (63) (4.31 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.23 (2H, ddd, J=7, 4, 4 Hz), 1.67 (2H, ddd, J=7, 4, 4 Hz), 7.09 (2x1H, d, J=8.4 Hz), 7.63 (2x1H, d, J=8.4 Hz);

MASS (ES-): m/e 287.

Preparation 64

Compound (64) was obtained from Compound (63) according to a manner similar to Preparation 6 (432 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.16 (2H, ddd, J=7, 4, 4 Hz), 1.45 (2H, ddd, J=7, 4, 4 Hz), 1.48 (3x3H, s), 6.49 (1H, d, J=15.7 Hz), 7.35 (2x1H, d, J=8 Hz), 7.53 (1H, d, J=15.7 Hz), 7.61 (2x1H, d, J=8 Hz);

MASS (ES-): m/e not determined.

Preparation 65

Compound (65) was obtained from Compound (64) according to a manner similar to Preparation 7 (1.67 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.20 (2H, m), 1.45 (3x3H, s), 1.51 (3x3H, s), 1.74 (2H, m), 6.40 (1H, d, J=15.7 Hz), 6.63 (1H, br-s), 6.98-7.62 (10H, m);

MASS (ES+): m/e 479.

Preparation 66

Compound (66) was obtained from Compound (65) according to a manner similar to Preparation 8 (710 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.71 (2H, m), 1.95 (2H, m), 6.59 (1H, d, J=15.8 Hz), 7.40-7.55 (4H, m), 7.63 (1H, d, J=15.8 Hz), 7.64-7.72 (2H, m), 7.76 (2x1H, d, J=8.4 Hz);

MASS (ES+): m/e 305.

Preparation 67

Compound (67) was obtained from Compound (66) according to a manner similar to Preparation 9 (647 mg). The Compound (67) was used in Example 26.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.39 (2H, m), 1.48-1.76 (8H, m), 3.34 (1H, m), 3.54 (1H, m), 3.96 (1H, m), 4.91 (2H, s), 6.51 (1H, d, J=16 Hz), 7.07-7.15 (2H, m), 7.31-7.43 (3H, m), 7.46-7.63 (4H, m);

MASS (ES+): m/e 404.

Preparation 68

To a stirred solution of 4-bromo-2-nitroaniline (1.37 g) in

dioxane (20 mL) was added 4-fluorophenylboronic acid (1.06 g), $PdCl_2(PPh_3)_2$ (133 mg), and 2M sodium carbonate solution (12.7 ml), and the mixture was stirred at 100°C for 2 hours. The solvent was evaporated and the residue was partioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The resulting solid was recrystalized from toluene to give Compound (68) (1.13 g) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 6.18 (2H, br-s), 6.89 (1H, d, J=8.7 Hz), 7.12 (2x1H, dd, J=8.7, 8.7 Hz), 7.51 (2x1H, dd, J=8.7, 5 Hz), 7.59 (1H, dd, J=8.7, 2.2 Hz), 8.31 (1H, d, J=2.2 Hz);

MASS (ES-) m/e 231.

Preparation 69

To a stirred solution of Compound (68) (1.08 g) in EtOH (15 mL) was added tin (II) chloride (1.32 g). The mixture was stirred at 100°C for 6 hours. The solvent was evaporated to the half volume and the residue was basified with 1N-NaOH to pH 9 and extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was triturated with ethyl acetate to give Compound (69) (800 mg) as an orange powder.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.45 (2x2H, br-s), 6.76 (2x1H, d, J=8.3 Hz), 6.89 (1H, d, J=2.1 Hz), 6.91 (1H, dd, J=8.3, 2.1 Hz), 7.06 (2x1H, dd, J=8.8, 8.8 Hz), 7.46 (2x1H, dd, J=8.8, 5.4 Hz);

MASS (ES+): m/e 203.

Preparation 70

Compound (70) was obtained from Compound (69) according to a manner similar to Preparation 7 (552 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (3x3H, s), 3.81 (2H, s), 6.39 (1H, sd, J=16 Hz), 6.80-7.62 (15H, m);

MASS (ES+): m/e 446.

Preparation 71

Compound (71) was obtained from Compound (70) according to a manner similar to Preparation 8 (375 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.56 (1H, d, J=16 Hz), 7.23-7.86 (11H, m), 7.94 (1H, s);

MASS (ES+): m/e 373.

Preparation 72

Compound (72) was obtained from Compound (71) according to a

manner similar to Preparation 9 (321 mg). The Compound (71) was used in Example 27.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.75 (6H, m), 3.52 (1H, m), 3.95 (1H, m), 4.22 (2H, s), 4.90 (1H, m), 6.48 (1H, d, J=15.8 Hz), 7.22-7.80 (12H, m), 11.23 (1H, br-s), 12.40 (H, br-s);

MASS (ES+): m/e 472.

Preparation 73

Compound (73) was obtained from Compound (6) according to a manner similar to Preparation 7 (228 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3x3H, s), 3.75-3.87 (4H, br), 6.41 (1H, d, J=15.7 Hz), 6.81-7.54 (13H, m), 7.58 (1H, d, J=15.7 Hz);

MASS (ES+): m/e 429.

Preparation 74

Compound (74) was obtained from Compound (73) according to a manner similar to Preparation 8 (165 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.59 (2H, s), 6.59 (1H, d, J=16 Hz), 7.38-7.55 (5H, m), 7.59 (1H, d, J=16 Hz), 7.67 (1H, m), 7.73 (2x1H, d, J=7.5 Hz), 7.78-7.85 (2H, m), 7.87 (1H, br), 7.96 (1H, br-s);

MASS (ES+): m/e 355.

Preparation 75

Compound (75) was obtained from Compound (74) according to a manner similar to Preparation 9 (185 mg). The Compound (75) was used in Example 28.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.53 (1H, m), 3.94 (1H, m), 4.23 (2H, s), 4.90 (1H, m), 6.50 (1H, d, J=16 Hz), 7.28-7.52 (10H, m), 7.57 (1H, m), 7.66 (2x1H, d, J=7.5 Hz), 11.25 (1H, br), 12.38 (1H, br);

MASS (ES+): m/e 454.

Preparation 76

Compound (76) was obtained according to a manner similar to Preparation 35 (320 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.24 (3H, s), 7.16 (1H, d, J=8.8 Hz), 7.68 (2H, s), 7.85-8.07 (5H, m), 8.34 (1H, d, J=2.5 Hz);

MASS (ES-): m/e 291.

Preparation 77

To a stirred solution of 4'-(methylsulfonyl)-3-nitro-1,1'-biphenyl-4-ylamine (305 g) in EtOH (15 mL) was added iron powder

(583 mg), NH_4Cl (56 mg) and water (1 mL). The mixture was refluxed for 5 hours. The iron powder was filtered off and the filtrate was evaporated in vacuo. The residue was partioned between $CHCl_3$ and saturated $NaHCO_3$ solution. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give Compound (77) (150 mg) as an orange powder.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.44 (3H, s), 4.45-5.20 (4H, m), 6.65 (1H, br), 6.82-7.22 (2H, m), 7.62-8.22 (4H, m);

MASS (ES+): m/e 263.

Preparation 78

Compound (78) was obtained from Compound (77) according to a manner similar to Preparation 7 (200 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (3x3H, s), 3.07 (3x1/2H, s), 3.08 (3x1/2H, s), 3.83 (2H, br-s), 6.39 (1H, d, J=16 Hz), 6.84-7.10 (2H, m), 7.29 (1H, m), 7.42 (2H, m), 7.53-7.73 (5H, m), 7.95 (2H, m);

MASS (ES+): m/e 507.

Preparation 79

Compound (79) was obtained from Compound (78) according to a manner similar to Preparation 8 (162 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.28 (3H, s), 4.59 (2H, s), 6.57 (1H, d, J=15.8 Hz), 7.52 (2x1H, d, J=8.2 Hz), 7.59 (1H, d, J=15.8 Hz), 7.74 (2x1H, d, J=8.2 Hz), 7.86-7.90 (2H, m), 7.95-8.10 (5H, m);

MASS (ES+): m/e 432.

Preparation 80

Compound (80) was obtained from Compound (79) according to a manner similar to Preparation 9 (190 mg). The Compound (80) was used for Example 29.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.25 (3H, s), 3.53 (1H, m), 3.94 (1H, m), 4.24 (2H, m), 4.90 (1H, m), 6.48 (1H, d, J=16 Hz), 7.39 (2x1H, d, J=8 Hz), 7.42-8.02 (10H, m), 11.23 (0.5H, br), 12.50 (0.5H, br);

MASS (ES+): m/e 532.

Preparation 81

Compound (81) was obtained from Compound (6) according to a manner similar to Preparation 7 (137 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7.5 Hz), 4.26 (2H, q, J=7.5 Hz), 4.38 (2H, s), 6.41 (1H, d, J=16 Hz), 7.18 (1H, dd, J=8, 4.5 Hz), 7.38 (2x1H, d, J=8 Hz), 7.51 (2x1H, d, J=8 Hz), 7.65 (1H,

d, J=16 Hz), 7.99-8.10 (2H, m);
MASS (ES+): m/e 308.

Preparation 82

Compound (82) was obtained from Compound (81) according to a manner similar to Preparation 12 (362 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.23 (2H, s), 6.50 (1H, d, J=16 Hz), 7.17 (1H, dd, J=8, 5 Hz), 7.38 (2x1H, d, J=8 Hz), 7.56 (1H, d, J=16 Hz), 7.65 (2x1H, d, J=8 Hz), 7.91 (1H, br), 8.25 (1H, br);
MASS (ES+): m/e 280.

Preparation 83

Compound (83) was obtained from Compound (82) according to a manner similar to Preparation 9 (312 mg). The Compound (83) was used in Example 30.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.21 (2H, br-s), 4.90 (1H, m), 6.48 (1H, d, J=15.5 Hz), 7.17 (1H, dd, J=8, 4.5 Hz), 7.39 (2x1H, d, J=8 Hz), 7.46 (1H, d, J=15.5 Hz), 7.54 (2x1H, br-d, J=8 Hz), 7.88 (1H, m), 8.27 (1H, m), 11.24 (1H, br-s), 12.58 (0.5H, br), 13.00 (0.5H, br);
MASS (ES+): m/e 379.

Preparation 84

Compound (84) was obtained from Compound (6) according to a manner similar to Preparation 7 (9.77 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26 (3H, t, J=7 Hz), 3.74 (2H, s), 4.19 (2H, q, J=7 Hz), 6.54 (2H, s), 6.62 (1H, d, J=16 Hz), 6.77 (1H, d, J=8.8 Hz), 7.41 (2x1H, d, J=8 Hz), 7.65 (1H, d, J=16 Hz), 7.70 (2x1H, d, J=8 Hz), 7.85 (1H, dd, J=8.8, 2.5 Hz), 8.20 (1H, d, J=2.5 Hz), 9.46 (1H, s);
MASS (ES+)::m/e 370.

Preparation 85

Compound (85) was obtained from Compound (84) according to a manner similar to Preparation 8 (6.83 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25 (3H, t, J=7 Hz), 4.18 (2H, q, J=7 Hz), 4.44 (2H, s), 6.64 (1H, d, J=16 Hz), 7.46 (2x1H, d, J=8 Hz), 7.64 (1H, d, J=16 Hz), 7.73 (2x1H, d, J=8 Hz), 7.80 (1H, d, J=9 Hz), 8.20 (1H, dd, J=9, 2.2 Hz), 8.50 (1H, d, J=2.2 Hz);
MASS (ES+): m/e 352.

Preparation 86

Compound (86) was obtained from Compound (85) according to a

manner similar to Preparation 77 (872 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.31 (3H, br-t, J=7 Hz), 4.15-4.36 (4H, m), 6.26 (1H, br-d, J=16 Hz), 6.64 (1H, m), 6.78 (1H, m), 7.20-7.40 (5H, m), 7.49 (1H, br-d, J=16 Hz);

MASS (ES+): m/e 322.

Preparation 87

To a stirred suspension of Compound (86) (303 mg) in dioxane (10 mL) was added di-tert-butyldicarbonate (618 mg) in dioxane (3mL) and then 1N-NaOH (2.8 mL), and the mixture was stirred at ambient temperature for 12 hours. The solvent was evaporated in vacuo and the residue was partioned between ethyl acetate and water. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (hexane : ethyl acetate = 1 : 1) to give Compound (87) (379 mg) as a pale brown amorphous (379 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.33 (3H, t, J=7 Hz), 1.52 (4.5H, s), 1.53 (4.5H, s), 1.58 (4.5H, s), 1.60 (4.5H, s), 4.25 (2H, q, J=7 Hz), 4.61 (2H, s), 6.39 (1H, d, J=16 Hz), 6.58 (1H, br-d, J=6 Hz), 7.09 (0.5H, dd, J=8.8, 2.2 Hz), 7.23-7.30 (2H, m), 7.42-7.48 (2.5H, m), 7.567.68 (2H, m), 7.77 (0.5H, d, J=8.8 Hz), 8.24 (0.5H, br);

MASS (ES+): m/e 522.

Preparation 88

To a stirred solution of Compound (87) (360 mg) in methanol (5 mL) was added 1N-NaOH solution (1.4 mL). The mixture was stirred at ambient temperature for 2.5 hours. The reaction mixture was neutralized by 1N-HCl solution, and the solvent was evaporated in vacuo. The residue was partioned between ethyl acetate and water. The oraganic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform :methanol = 10 : 1) to give Compound (88) (57 mg) as an orange powder and a methyl ester of Compound (88) as a by-product.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48 (3x3H, s), 4.16 (2H, s), 6.49 (1H, d, J=16 Hz), 7.12 (1H, br), 7.31-7.42 (3H, m), 7.55 (1H, d, J=16 Hz), 7.60-7.72 (3H, m), 9.25 (1H, br), 12.12 (1H, br);

MASS (ES+): m/e 394.

Preparation 89

Compound (89) was obtained from the metyl ester of Compound

(88) according to a manner similar to Preparation 12 (245 mg).
[The Compound (89) is similar to Compound (88).]
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48 (3x3H, s), 4.22 (2H, s), 6.50 (1H, d, J=16 Hz), 7.19 (1H, br-d, J=8.5 Hz), 7.34-7.42 (3H, m), 7.56 (1H, d, J=16 Hz), 7.65 (2x1H, d, J=8.5 Hz), 7.72 (1H, br-s), 9.30 (1H, br-s), 12.38 (1H, br);
MASS (ES+): m/e 394.

Preparation 90

Compound (90) was obtained from Compound (88) according to a manner similar to Preparation 9 (230 mg). The Compound (90) was used for Example 31.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.48 (3x3H, s), 1.48-1.75 (6H, m), 3.53 (1H, m), 3.94 (1H, m), 4.15 (2H, s), 4.90 (1H, m), 6.47 (1H, br-d, J=16 Hz), 7.06-7.414 (4H, m), 7.46 (1H, d, J=16 Hz), 7.53 (2x1H, br-d, J=8.5 Hz), 7.67 (1H, m), 9.15 (1/3H, br-s), 9.26 (2/3H, br-s), 11.22 (1H, br-s), 12.10 (2/3H, br-s), 12.13 (1/3H, br-s);
MASS (ES+): m/e 493.

Preparation 91

To a stirred solution of Compound (86) (150 mg) in DMF (2 mL) was added butyric acid (49 mg), HOBT (76 mg), and EDCI hydrochloride (107 mg), and the resulting mixture was stirred at ambient temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and washed successively with water, saturated $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol = 10 : 1) to give Compound (91) (30 mg) as a pale yellow amorphous.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.98 (3H, t, J=7.3 Hz), 1.33 (3H, t, J=7 Hz), 1.73 (2H, tq, J=7.3, 7.3 Hz), 2.33 (2H, t, J=7.3 Hz), 4.09 (2H, s), 4.24 (2H, q, J=7 Hz), 6.31 (1H, d, J=16 Hz), 7.05 (1H, br-d, J=8 Hz), 7.15 (2x1H, d, J=8 Hz), 7.32 (2x1H, d, J=8 Hz), 7.36 (1H, d, J=8 Hz), 7.53 (1H, s), 7.58 (1H, s);
MASS (ES+): m/e 392.

Preparation 92

Compound (92) was obtained from Compound (91) according to a manner similar to Preparation 11 (28 mg).
^{1}H-NMR (300 MHz, CD_3OD, δ): 1.00 (3H, t, J=7.3 Hz),1.73 (2H, tq, J=7.3, 7.3 Hz), 2.42 (2H, t, J=7.3 Hz), 4.58 (2H, s), 6.52 (1H, d,

J=16 Hz), 7.47-7.58 (3H, m), 7.64-7.74 (4H, m), 8.29 (1H, s);
MASS (ES+): m/e 364.

Preparation 93

Compound (93) was obtained from Compound (92) according to a manner similar to Preparation 9 (19 mg). The Compound (93) was used in Example 32.

^{1}H-NMR (300 MHz, CD_3OD-$CDCl_3$, δ): 1.00 (3H, t, J=7.4 Hz), 1.52-1.96 (8H, m), 2.35 (2H, t, J=7.5 Hz), 3.65 (1H, m), 4.03 (1H, m), 4.11 (2H, s), 5.03 (1H, m), 6.24 (1H, m), 7.06-7.29 (4H, m), 7.38 (2x1H, d, J=8.5 Hz), 7.48 (1H, m), 7.82 (1H, s);
MASS (ES+): m/e 463.

Preparation 94

Compound (94) was obtained from Compound (6) according to a manner similar to Preparation 7 (641 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26 (3H, t, J=7 Hz), 3.76 (2H, s), 4.19 (2H, q, J=7 Hz), 6.62 (1H, d, J=16 Hz), 6.64 (1H, dd, J=8.5, 8.5 Hz), 7.12 (2H, s), 7.40 (2x1H, d, J=8.5 Hz), 7.45 (1H, dd, J=8.5, 1 Hz), 7.65 (1H, d, J=16 Hz), 7.69 (2x1H, d, J=8.5 Hz), 7.91 (1H, dd, J=8.5, 1 Hz), 9.57 (1H, s);
MASS (ES+): m/e 370.

Preparation 95

Compound (95) was obtained from Compound (94) according to a manner similar to Preparation 8 (512 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25 (3H, t, J=7 Hz), 4.18 (2H, q, J=7 Hz), 4.45 (2H, s), 6.62 (1H, d, J=16 Hz), 7.46 (2x1H, d, J=8.3 Hz), 7.49 (1H, dd, J=8, 8 Hz), 7.63 (1H, d, J=16 Hz), 7.71 (2x1H, d, J=8.3 Hz), 8.11 (1H, d, J=8 Hz), 8.20 (1H, d, J=8 Hz);
MASS (ES+): m/e 352.

Preparation 96

Compound (96) was obtained from Compound (95) according to a manner similar to Preparation 12 (119 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.34 (2H, s), 6.49 (1H, d, J=16 Hz), 7.36 (1H, dd, J=8, 8 Hz), 7.41 (2x1H, d, J=8 Hz), 7.55 (1H, d, J=16 Hz), 7.64 (2x1H, d, J=8 Hz), 8.04 (1H, d, J=8 Hz), 8.09 (1H, d, J=8 Hz), 13.26 (1H, br-s);
MASS (ES+): m/e 324.

Preparation 97

Compound (97) was obtained from Compound (96) according to a

manner similar to Preparation 9 (70 mg). The Compound (97) was used in Example 33.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.77 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.34 (2H, s), 4.90 (1H, m), 6.47 (1H, d, J=16 Hz), 7.37 (1H, dd, J=8, 8 Hz), 7.42 (2x1H, d, J=8 Hz), 7.46 (1H, d, J=16 Hz), 7.53 (2x1H, d, J=8 Hz), 8.05 (1H, d, J=8 Hz), 8.10 (1H, d, J=8 Hz);
MASS (ES+): m/e 423.

Preparation 98

Compound (98) was obtained from Compound (6) according to a manner similar to Preparation 7 (160 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26 (3H, t, J=7 Hz), 3.75 (2H, s), 4.19 (2H, q, J=7 Hz), 6.47 (2H, br-s), 6.62 (1H, d, J=16 Hz), 6.70 (1H, d, J=6 Hz), 7.40 (2x1H, d, J=8 Hz), 7.65 (1H, d, J=16 Hz), 7.69 (2x1H, d, J=8 Hz), 7.91 (1H, d, J=6 Hz), 8.18 (1H, s), 9.61 (1H, s);
MASS (ES+): m/e 326.

Preparation 99

Compound (99) was obtained from Compound (6) according to a manner similar to Preparation 8 (91 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.26 (2H, s), 6.50 (1H, d, J=16 Hz), 7.38 (2x1H, d, J=8 Hz), 7.48 (1H, m), 7.56 (1H, d, J=16 Hz), 7.65 (2x1H, d, J=8 Hz), 8.25 (1H, d, J=3 Hz), 8.81 (1H, s), 12.75 (1H, br);
MASS (ES+): m/e 280.

Preparation 100

Compound (100) was obtained from Compound (99) according to a manner similar to Preparation 9 (33 mg). The Compound (100) was used for Example 34.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.40-1.80 (6H, m), 3.52 (1H, m), 3.96 (1H, m), 4.26 (2H, s), 4.91 (1H, m), 6.50 (1H, br-d, J=15.5 Hz), 7.35-7.60 (6H, m), 8.22 (1H, d, J=5.5 Hz), 8.81 (1H, s);
MASS (ES+) m/e 379.

Preparation 101

Compound (101) was obtained from Compound (6) according to a manner similar to Preparation 7 (520 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.26 (3H, t, J=7 Hz), 3.11 (3H, s), 3.31 (3H, s), 3.62 (2H, s), 4.19 (2H, q, J=7 Hz), 6.54-6.68 (3H, m), 7.41 (2x1H, d, J=8 Hz), 7.58-7.70 (3H, m), 8.66 (1H, s);

MASS (ES+): m/e 387.

Preparation 102

Compound (102) was obtained from Compound (101) according to a manner similar to Preparation 8 (416 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.22 (3H, s), 3.40 (3H, s), 4.08 (2H, s), 6.49 (1H, d, J=16 Hz), 7.33 (2x1H, d, J=8.3 Hz), 7.55 (1H, d, J=16 Hz), 7.64 (2x1H, d, J=8.3 Hz), 12.39 (1H, s), 13.48 (1H, s);
MASS (ES+): m/e 341.

Preparation 103

Compound (103) was obtained from Compound (102) according to a manner similar to Preparation 9 (254 mg). The Compound (103) was used in Example 35.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.76 (6H, m), 3.22 (3H, s), 3.40 (3H, s), 3.53 (1H, m), 3.95 (1H, m), 4.07 (2H, s), 4.90 (1H, m), 6.47 (1H, d, J=16 Hz), 7.33 (2x1H, d, J=7.5 Hz), 7.46 (1H, d, J=16 Hz), 7.53 (2x1H, d, J=7.5 Hz), 11.23 (1H, br-s), 13.47 (1H, br-s);
MASS (ES-): m/e 438.

Preparation 104

Compound (104) was obtained from Compound (85) according to a manner similar to Preparation 12 (1.54 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.38 (2H, s), 6.52 (1H, d, J=16.2 Hz), 7.42 (2x1H, d, J=8 Hz), 7.57 (1H, d, J=16.2 Hz), 7.68 (2x1H, d, J=8 Hz), 7.74 (1H, d, J=8.8 Hz), 8.14 (1H, dd, J=8.8, 2.2 Hz), 8.46 (1H, d, J=2.2 Hz);
MASS (ES+): m/e 324.

Preparation 105

Compound (105) was obtained from Compound (104) according to a manner similar to Preparation 9 (1.42 g). The Compound (105) was used in Example 36.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.76 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.30 (2H, s), 4.90 (1H, m), 6.48 (1H, d, J=15.8 Hz), 7.39 (2x1H, d, J=8.5 Hz), 7.47 (1H, d, J=15.8 Hz), 7.55 (2x1H, d, J=8.5 Hz), 7.67 (1H, d, J=8.8 Hz), 8.08 (2x1H, d, J=8.8 Hz), 8.41 (1H, d, J=2.2 Hz), 11.25 (1H, br), 13.02 (1H, br);
MASS (ES+): m/e 423.

Preparation 106

Thionyl chloride (1.75 mL) was dropwise added under stirring to methanol at 0°C. After 30 minutes 4-hydroxycinnamic acid (3.29

g) was added and the mixture was refluxed for 1.5 h. The solvent was evaporated in vacuo and the residue was crystalized from diisopropyl ether and hexane to give Compound (106) (2.41 g) as a white crystal.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.80 (3H, s), 5.44 (1H, s), 6.31 (1H, d, J=16 Hz), 6.85 (2x1H, d, J=8.5 Hz), 7.43 (2x1H, d, J=8.5 Hz), 7.64 (1H, d, J=16 Hz);

MASS (ES-): m/e 177.

Preparation 107

To a stirred solution of Compound (106) (609 mg) in dimethylformamide (15 mL) was added sodium hydride (164 mg, 60% oil dispersion) at 0°C. After 30 minutes, tert-butyl bromoacetate (733 mg) was added dropwise, and the mixture was stirred at ambient temperature for 2 hours. The resulting mixture was poured into 10% citric acid solution and extracted with ethyl acetate. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography (hexane : ethyl acetate = 4 : 1) to give Compound (107) (962 mg) as a solid.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49 (3x3H, s), 3.80 (3H, s), 4.55 (2H, s), 6.32 (1H, d, J=15.8 Hz), 6.90 (2x1H, d, J=8.8 Hz), 7.47 (2x1H, d, J=8.8 Hz), 7.65 (1H, d, J=15.8 Hz);

MASS (ES+): m/e not detected.

Preparation 108

A solution of Compound (107) (906 mg) in 0.5 N-hydrogen chloride in acetic acid (10 mL) was heated at 60°C for 2 hours. The solvent was evaporated in vacuo and the residue was triturated with diisopropyl ether to give Compound (108) (645 mg) as a white solid.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.71 (3H, s), 4.74 (2H, s), 6.51 (1H, d, J=16 Hz), 6.96 (2x1H, d, J=8.5 Hz), 7.62 (1H, d, J=16 Hz), 7.67 (2x1H, d, J=8.5 Hz), 13.07 (1H, br-s);

MASS (ES-): m/e 235.

Preparation 109

Compound (109) was obtained from Compound (108) according to a manner similar to Preparation 7 (950 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45 (3x3H, s), 3.71 (3H, s), 4.79 (2H, s), 6.53 (1H, d, J=16 Hz), 7.07 (2x1H, d, J=8.8 Hz), 7.08-7.20 (2H,

m), 7.46 (1H, m), 7.56 (1H, m), 7.63 (1H, d, J=16 Hz), 7.72 (2x1H, d, J=8.8 Hz), 8.73 (1H, br-s), 9.55 (1H, br-s);
MASS (ES+): m/e 427.

Preparation 110

Compound (110) was obtained from Compound (109) according to a manner similar to Preparation 8 (800 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.71 (3H, s), 5.69 (2H, s), 6.56 (1H, d, J=16 Hz), 7.20 (2x1H, d, J=8.8 Hz), 7.49-7.57 (2H, m), 7.65 (1H, d, J=16 Hz), 7.73-7.85 (4H, m);
MASS (ES+): m/e 309.

Preparation 111

Compound (111) was obtained from Compound (110) according to a manner similar to Preparation 12 (580 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.45 (2H, s), 6.41 (1H, d, J=16 Hz), 7.14 (2x1H, d, J=8.8 Hz), 7.23-7.32 (2H, m), 7.55 (1H, d, J=16 Hz), 7.56-7.66 (2H, m), 7.68 (2x1H, d, J=8.8 Hz), 12.28 (1H, br);
MASS (ES+): m/e 295.

Preparation 112

Compound (112) was obtained from Compound (111) according to a manner similar to Preparation 9 (503 mg). The Compound (112) was used in Example 37.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.47-1.76 (6H, m), 3.53 (1H, m), 3.95 (1H, m), 4.89 (1H, m), 5.37 (2H, s), 6.37 (1H, d, J=16 Hz), 7.10-7.25 (4H, m), 7.39-7.67 (5H, m), 11.16 (1H, s), 12.68 (1H, s);
MASS (ES+): m/e 394.

Preparation 113

To a stirred solution of Compound (86) (165 mg) in methanol (3 mL) were added cyclopentanone (52 mg) and sodium cyanoborohydride (39 mg). To the mixture was added acetic acid so that final pH was set to 5. The mixture was stirred at ambient temperature for 2 hours. The resulting mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by preparative thin layer chromatography (chloroform : methanol = 10 : 1) to give Compound (113) (140 mg) as a brown oil.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7.3 Hz), 1.40-1.77 (6H, m), 1.95-2.08 (2H, m), 3.76 (1H, m), 4.24 (2H, s), 4.26 (2H, q,

J=7.3 Hz), 6.41 (1H, d, J=16 Hz), 6.56 (1H, dd, J=7, 2.2 Hz), 6.64 (1H, s), 7.31 (2x1H, d, J=8 Hz), 7.36 (1H, d, J=8.8 Hz), 7.48 (2x1H, d, J=8 Hz), 7.65 (1H, d, J=16 Hz);
MASS (ES+): m/e 390.

Preparation 114

Compound (114) was obtained from Compound (113) according to a manner similar to Preparation 12 (91 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.36-1.76 (6H, m), 1.89 (2H, m), 4.08 (2H, s), 6.44-6.56 (3H, m), 7.17 (1H, m), 7.34 (2x1H, d, J=8 Hz), 7.55 (1H, d, J=16 Hz), 7.62 (2x1H, d, J=8 Hz), 11.72 (1H, br);
MASS (ES+): m/e 362.

Preparation 115

Compound (115) was obtained from Compound (114) according to a manner similar to Preparation 9 (40 mg). The Compound (115) was used in Example 38.
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.38-2.08 (14H, m), 3.62 (1H, m), 3.75 (1H, m), 4.00 (1H, m), 4.11 (2H, s), 5.08 (1H, m), 6.20 (1H, br), 6.56 (1H, d, J=8 Hz), 6.68 (1H, s), 6.94-7.55 (6H, m);
MASS (ES+): m/e 461.

Preparation 116

Compound (116) was obtained according to a manner similar to Preparation 106 (1.77 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.72 (3H, s), 6.53 (1H, d, J=16 Hz), 6.84 (1H, br-dd, J=8, 2 Hz), 7.04 (1H, br-d, J=2 Hz), 7.14 (1H, br-d, J=8 Hz), 7.22 (1H, dd, J=8, 8 Hz), 7.57 (1H, d, J=16 Hz), 9.63 (1H, s);
MASS (ES-): m/e 177.

Preparation 117

Compound (117) was obtained from Compound (116) according to a manner similar to Preparation 107 (1.61 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49 (3x3H, s), 3.81 (3H, s), 4.54 (2H, s), 6.41 (1H, d, J=16 Hz), 6.92 (1H, dd, J=8, 2.5 Hz), 7.04 (1H, dd, J=2.5, 2.5 Hz), 7.15 (1H, br-d, J=8 Hz), 7.31 (1H, dd, J=8, 8 Hz), 7.64 (1H, d, J=16 Hz);
MASS (ES+): m/e not detected.

Preparation 118

Compound (118) was obtained from Compound (117) according to a manner similar to Preparation 8 (1.25 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.82 (3H, s), 4.72 (2H, s), 6.43 (1H, d, J=16 Hz), 6.96 (1H, dd, J=8, 2.5 Hz), 7.07 (1H, br-s), 7.20 (1H, br-d, J=8 Hz), 7.34 (1H, dd, J=8, 8 Hz), 7.65 (1H, d, J=16 Hz);
MASS (ES-): m/e 235.

Preparation 119

Compound (119) was obtained from Compound (118) according to a manner similar to Preparation 7 (1.92 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.49 (3x3H, s), 3.82 (3H, s), 4.69 (2H, s), 6.45 (1H, d, J=16 Hz), 6.69 (1H, br-s), 7.03 (1H, dd, J=8, 2.5 Hz), 7.15-7.26 (4H, m), 7.37 (1H, dd, J=8, 8 Hz), 7.41 (1H, m), 7.63 (1H, m), 7.66 (1H, d, J=16 Hz), 9.00 (1H, br-s);
MASS (ES+): m/e 427.

Preparation 120

Compound (120) was obtained from Compound (119) according to a manner similar to Preparation 8 (1.67 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.74 (3H, s), 5.68 (2H, s), 6.74 (1H, d, J=16 Hz), 7.21 (1H, m), 7.40-7.46 (2H, m), 7.49-7.59 (3H, m), 7.68 (1H, d, J=16 Hz), 7.77-7.85 (2H, m);
MASS (ES+): m/e 309.

Preparation 121

Compound (121) was obtained from Compound (120) according to a manner similar to Preparation 12 (1.24 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.37 (2H, s), 6.58 (1H, d, J=16 Hz), 7.11-7.26 (3H, m), 7.27-7.40 (2H, m), 7.45 (1H, br-s), 7.50 (1H, m), 7.57 (1H, d, J=16 Hz), 7.63 (1H, m), 12.69 (1H, s);
MASS (ES+): m/e 295.

Preparation 122

Compound (122) was obtained from Compound (120) according to a manner similar to Preparation 9 (1662 mg). The Compound (122) was used in Example 39.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.46-1.78 (6H, m), 3.54 (1H, m), 3.96 (1H, m), 4.91 (1H, m), 5.36 (2H, s), 6.53 (1H, d, J=16 Hz), 7.12 (1H, dd, J=8, 2.5 Hz), 7.15-7.26 (3H, m), 7.32 (1H, br-s), 7.36 (1H, dd, J=8, 8 Hz), 7.46-7.68 (2H, m), 7.47 (1H, d, J=16 Hz), 11.27 (1H, br-s), 12.69 (1H, br-s);
MASS (ES+): m/e 394.

Preparation 123

Compound (123) was obtained from Compound (86) according to

a manner similar to Preparation 113 (415 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.12 (2x3H, t, J=7 Hz), 1.34 (3H, t, J=7 Hz), 3.34 (2x2H, q, J=7 Hz), 4.23 (2H, s), 4.26 (2H, q, J=7 Hz), 6.39 (1H, d, J=16 Hz), 6.79 (1H, dd, J=9, 2 Hz), 6.91 (1H, d, J=2 Hz), 7.30 (2x1H, d, J=8 Hz), 7.44 (1H, d, J=9 Hz), 7.45 (2x1H, d, J=8 Hz), 7.63 (1H, d, J=16 Hz);

MASS (ES+): m/e 378.

Preparation 124

Compound (124) was obtained from Compound (123) according to a manner similar to Preparation 12 (227 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.05 (2x3H, t, J=7 Hz), 3.28 (2x2H, q, J=7 Hz), 4.12 (2H, s), 6.49 (1H, d, J=16 Hz), 6.61-6.72 (2H, m), 7.28 (1H, br-d, J=8 Hz), 7.35 (2x1H, d, J=8 Hz), 7.56 (1H, d, J=16 Hz), 7.63 (2x1H, d, J=8 Hz), 11.82 (1H, br-s);

MASS (ES+): m/e 350.

Preparation 125

Compound (125) was obtained from Compound (124) according to a manner similar to Preparation 9 (132 mg). The Compound (125) was used in Example 40.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.12 (2x3H, t, J=7 Hz), 1.50-1.92 (6H, m), 3.32 (2x3H, q, J=7 Hz), 3.62 (1H, m), 4.00 (1H, m), 4.15 (2H, br-s), 5.07 (1H, m), 6.22 (1H, br), 6.71-6.83 (2H, m), 6.96-7.28 (3H, m), 7.38-7.54 (3H, m);

MASS (ES+): m/e 449.

Preparation 126

Compound (126) was obtained according to a manner similar to Preparation 106 (4.19 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.80 (3H, s), 3.93 (3H, s), 5.85 (1H, br-s), 6.30 (1H, d, J=16 Hz), 6.92 (1H, d, J=8 Hz), 7.03 (1H, d, J=2 Hz), 7.08 (1H, dd, J=8, 2 Hz), 7.63 (1H, d, J=16 Hz);

MASS (ES+) : m/e not detected.

Preparation 127

Compound (127) was obtained from Compound (126) according to a manner similar to Preparation 107 (5.16 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.47 (3x3H, s), 3.80 (3H, s), 3.92 (3H, s), 4.62 (2H, s), 6.32 (1H, d, J=16 Hz), 6.76 (1H, d, J=8.7 Hz), 7.04-7.09 (2H, m), 7.63 (1H, d, J=16 Hz);

MASS (ES+): m/e not detected.

Preparation 128

Compound (128) was obtained from Compound (127) according to a manner similar to Preparation 8 (4.28 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.81 (3H, s), 3.93 (3H, s), 4.74 (2H, s), 6.35 (1H, d, J=16 Hz), 6.89 (1H, d, J=9 Hz), 7.07-7.12 (2H, m), 7.63 (1H, d, J=16 Hz);

MASS (ES-): m/e 265.

Preparation 129

Compound (129) was obtained from Compound (128) according to a manner similar to Preparation 7 (5.43 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.42 (3x3H, s), 3.72 (3H, s), 3.86 (3H, s), 4.76 (2H, s), 6.61 (1H, d, J=16 Hz), 7.02 (1H, d, J=8.5 Hz), 7.08-7.19 (2H, m), 7.25 (1H, dd, J=8.5, 2 Hz), 7.40-7.48 (2H, m), 7.57-7.66 (2H, m), 8.71 (1H, s), 9.46 (1H, s);

MASS (ES+): m/e 457.

Preparation 130

Compound (130) was obtained from Compound (129) according to a manner similar to Preparation 8 (4.35 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.72 (3H, s), 3.85 (3H, s), 5.67 (2H, s), 6.65 (1H, d, J=16 Hz), 7.20-7.32 (2H, m), 7.49 (1H, s), 7.54-7.62 (2H, m), 7.63 (1H, d, J=16 Hz), 7.80-7.88 (2H, m);

MASS (ES+): m/e 339.

Preparation 131

Compound (131) was obtained from Compound (130) according to a manner similar to Preparation 12 (1.63 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.83 (3H, s), 5.33 (2H, s), 6.47 (1H, d, J=16 Hz), 7.14-7.26 (4H, m), 7.36 (1H, s), 7.50 (1H, m), 7.52 (1H, d, J=16 Hz), 7.63 (1H, m), 12.70 (1H, s);

MASS (ES+): m/e 325.

Preparation 132

Compound (132) was obtained from Compound (131) according to a manner similar to Preparation 9 (1.93 g). The Compound (132) was used in Example 41.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.45-1.77 (6H, m), 3.53 (1H, m), 3.82 (3H, s), 3.95 (1H, m), 4.90 (1H, m), 5.32 (2H, s), 6.41 (1H, d, J=16 Hz), 7.10-7.28 (5H, m), 7.43 (1H, d, J=16 Hz), 7.50 (1H, m), 7.62 (1H, m), 11.13 (1H, s), 12.69 (1H, s);

MASS (ES+): m/e 424.

Preparation 133

Compound (133) was obtained from Compound (86) according to a manner similar to Preparation 113 (437 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7 Hz), 2.92 (2x3H, s), 4.21 (2H, s), 4.26 (2H, q, J=7 Hz), 6.39 (1H, d, J=16 Hz), 6.75-6.84 (2H, m), 7.24-7.32 (2H, m), 7.42-7.50 (3H, m), 7.63 (1H, d, J=16 Hz);

MASS (ES+): m/e 350.

Preparation 134

The ethylcarbonyl group of Compound (133) was deprotected according to a manner similar to Preparation 12. The obtained compound (300 mg) was suspended in dioxane (10 mL). To the suspension was added 1N-NaOH (3 mL) di-tert-butyldicarbonate (407 mg) in dioxane (4mL) and the mixture was stirred at ambient temperature for 12 hours. Additional di-tert-butyldicarbonate (407 mg) and 1N-NaOH (3 mL) was added and the mixture was stirred at ambient temperature for 6 hours. The solvent was evaporated in vacuo and the residue was partioned between diisopropyl ether and water. The aqueous phase was acidified with hydrochloric acid to pH 5 and the precipitate was collected and washed with water to give Compound (134) (326 mg) as a pale brown powder. The obtained compound (134) was used in Example 42.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.45-1.95 (15H, m), 2.94-3.03 (6H, m), 3.65 (1H, m), 3.96 (1H, m), 4.54-4.64 (2H, m), 5.00 (1H, m), 6.30-7.80 (9H, m);

MASS (ES+) m/e 521.

Preparation 135

Compound (135) was obtained according to a manner similar to Preparation 106 (2.11 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.79 (3H, s), 3.93 (3H, s), 6.30 (1H, d, J=16 Hz), 6.85 (1H, d, J=8 Hz), 7.03 (1H, dd, J=8, 2 Hz), 7.14 (1H, d, J=2 Hz), 7.60 (1H, d, J=16 Hz);

MASS (ES+): m/e 209.

Preparation 136

Compound (136) was obtained from Compound (135) according to a manner similar to Preparation 107 (3.12 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.48 (3x3H, s), 3.79 (3H, s), 3.91 (3H, s), 4.61 (2H, s), 6.26 (1H, d, J=16 Hz), 6.89 (1H, d, J=8.3 Hz),

6.97 (1H, d, J=2 Hz), 7.14 (1H, dd, J=8.3, 2 Hz), 7.60 (1H, d, J=16 Hz);
MASS (ES+): m/e 323.

Preparation 137

Compound (137) was obtained from Compound (136) according to a manner similar to Preparation 8 (2.03 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.71 (3H, s), 3.81 (3H, s), 4.75 (2H, s), 6.54 (1H, d, J=16 Hz), 7.01 (1H, d, J=8 Hz), 7.27 (1H, dd, J=8, 2 Hz), 7.31 (1H, d, J=2 Hz), 7.57 (1H, d, J=16 Hz), 12.87 (1H, br);
MASS (ES+): m/e 267.

Preparation 138

Compound (138) was obtained from Compound (137) according to a manner similar to Preparation 8 (2.97 g).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.47 (3x3H, s), 3.80 (3H, s), 3.93 (3H, s), 4.72 (2H, s), 6.33 (1H, d, J=16 Hz), 6.95 (1H, d, J=8 Hz), 6.96 (1H, br), 7.12-7.29 (4H, m), 7.47 (1H, br-d, J=7.5 Hz), 7.62 (1H, d, J=16 Hz), 7.64 (1H, br-d, J=7.5 Hz), 9.02 (1H, s);
MASS (ES+) m/e 457.

Preparation 139

Compound (139) was obtained from Compound (138) according to a manner similar to Preparation 7 (2.29 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.71 (3H, s), 3.83 (3H, s), 5.63 (2H, s), 6.61 (1H, d, J=16 Hz), 7.11 (1H, d, J=8.4 Hz), 7.42 (1H, dd, J=8.4, 2 Hz), 7.50-7.58 (2H, m), 7.61 (1H, d, J=16 Hz), 7.65 (1H, d, J=2 Hz), 7.78-7.96 (2H, m);
MASS (ES+) m/e 339.

Preparation 140

Compound (140) was obtained from Compound (139) according to a manner similar to Preparation 12 (1.84 g).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.81 (3H, s), 5.36 (2H, s), 6.45 (1H, d, J=16 Hz), 7.04 (1H, d, J=8.8 Hz), 7.20-7.28 (2H, m), 7.28 (1H, dd, J=8.8, 2 Hz), 7.52 (1H, d, J=16 Hz), 7.55-7.64 (2H, m), 7.57 (1H, d, J=2 Hz), 12.26 (1H, br-s);
MASS (ES+) m/e 325.

Preparation 141

Compound (141) was obtained from Compound (140) according to a manner similar to Preparation 9 (609 mg). The Compound (141) was used in Example 43.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.42-1.78 (6H, m), 3.53 (1H, m), 3.81 (3H, s), 3.96 (1H, m), 4.90 (1H, m), 5.32 (2H, s), 6.40 (1H, br-d, J=16 Hz), 7.05 (1H, d, J=8.4 Hz), 7.16-7.26 (3H, m), 7.36-7.47 (2H, m), 7.50-7.66 (2H, m), 11.18 (1H, br), 12.69 (1H, br);
MASS (ES+) m/e 424.

Preparation 142

Compound (142) was obtained from Compound (6) according to a manner similar to Preparation 7 (400 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (9H, s), 3.76 (2H, s), 5.86 (2H, s), 6.33 (1H, s), 6.38 (1H, d, J=16.1 Hz), 6.77 (1H, s), 7.37 (2H, d, J=8.1 Hz), 7.54 (2H, d, J=8.1 Hz), 7.58 (1H, d, J=16.5 Hz);
MASS (ES+): m/e 397 (M+1).

Preparation 143

Compound (143) was obtained from Compound (142) according to a manner similar to Preparation 8 (305 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.44 (2H, s), 6.15 (2H, s), 6.55 (1H, d, J=16.2 Hz), 7.29 (2H, s), 7.42 (2H, d, J=8.1 Hz), 7.58 (1H, d, J=15.7 Hz), 7.72 (2H, d, J=8.4 Hz);
MASS (ES+): m/e 323 (M+1).

Preparation 144

Compound (144) was obtained from Compound (143) according to a manner similar to Preparation 9 (196 mg). The Compound (144) was used in Example 44.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.69 (3H, br), 3.53 (1H, m), 3.95 (1H, m), 4.11 (2H, s), 4.90 (1H, s), 5.95 (2H, s), 6.46 (1H, d, J=15.4 Hz), 6.96 (1H, s), 7.03 (1H, s), 7.34 (2H, d, J=8.1 Hz), 7.46 (1H, d, J=15.8 Hz), 7.52 (2H, d, J=8.1 Hz);
MASS (ES+): m/e 422 (M+1).

Preparation 145

Compound (145) was obtained from Compound (6) according to a manner similar to Preparation 7 (460 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): (1:1 mixture) 1.54 (9H, s), 3.71 (3H, s), 3.82 (2H, s), 6.30 (1H, d, J=8.1 Hz), 6.39 (1H, d, J=16.1 Hz), 6.41 (1H, d, J=8.0 Hz), 6.98 (1H, t, J=8.4 Hz), 7.40 (2H, d, J=8.4 Hz), 7.54 (2H, d, J=8.4 Hz), 7.59 (1H, d, J=15.7 Hz), 1.54 (9H, s), 3.77 (2H, s), 3.83 (3H, s), 6.37 (1H, d, J=15.8 Hz), 6.65-6.74 (sH, m), 6.80 (1H, dd, J=7.7,1.8 Hz), 7.37 (2H, d, J=8.4 Hz), 7.53 (2H, d, J=8.4 Hz), 7.57 (1H, d, J=17.2 Hz);

MASS (ES+): m/e 383 (M+1).

Preparation 146

Compound (146) was obtained from Compound (145) according to a manner similar to Preparation 8 (326 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.00 (3H, s), 4.44 (2H, s), 6.54 (1H, d, J=15.7 Hz), 7.06 (1H, d, J=8.7 Hz), 7.24 (1H, d, J=8.1 Hz), 7.40 (1H, t, J=8.1 Hz), 7.44 (2H, d, J=8.4 Hz), 7.58 (1H, d, J=16.0 Hz), 7.71 (2H, d, J=8.2 Hz);

MASS (ES+): m/e 309 (M+1).

Preparation 147

Compound (147) was obtained from Compound (146) according to a manner similar to Preparation 9 (308 mg). The Compound (147) was used in Example 45.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.53 (3H, br), 1.69 (3H, br), 3.52 (1H, m), 3.90 (3H, s), 3.95 (1H, m), 4.15 (2H, s), 4.90 (1H, s), 6.46 (1H, d, J=16.2 Hz), 6.68 (1H, br), 7.04 (2H, m), 7.35 (2H, d, J=8.0 Hz), 7.45 (1H, d, J=16.4 Hz), 7.52 (2H, d, J=8.0 Hz);

MASS (ES+): m/e 408 (M+1).

Preparation 148

Compound (148) was obtained according to a manner similar to Preparation 6 (929 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.50 (3H, d, J=6.9 Hz), 1.53 (9H, s), 3.75 (1H, q, J=7.1 Hz), 6.33 (1H, d, J=16.1 Hz), 7.32 (2H, d, J=8.5 Hz), 7.45 (2H, d, J=8.1 Hz), 7.55 (1H, d, J=16.1 Hz);

MASS (ES+): not detected.

Preparation 149

Compound (149) was obtained from Compound (148) according to a manner similar to Preparation 7 (1.09 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (9H, s), 1.60 (3H, d, J=7.0 Hz), 3.79 (1H, q, J=7.0 Hz), 6.36 (1H, d, J=16.0 Hz), 6.70-6.78 (2H, m), 6.98-7.04 (1H, m), 7.08-7.15 (1H, m), 7.40 (2H, d, J=8.6 Hz), 7.51 (2H, d, J=8.4 Hz), 7.56 (1H, d, J=16.0 Hz);

MASS (ES+): m/e 367 (M+1).

Preparation 150

Compound (150) was obtained from Compound (149) according to a manner similar to Preparation 8 (567 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.86 (3H, d, J=7.0 Hz), 4.83 (1H, q, J=7.0 Hz), 6.55 (1H, d, J=15.8 Hz), 7.49 (2H, d, J=8.1 Hz), 7.52-

7.55 (2H, m), 7.58 (1H, d, J=16.4 Hz), 7.73 (2H, d, J=8.1 Hz), 7.76-7.79 (2H, m);
MASS (ES+): m/e 293 (M+1).

Preparation 151

Compound (151) was obtained from Compound (150) according to a manner similar to Preparation 9 (598 mg). The Compound (151) was used in Example 46.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.68 (3H, br), 1.70 (3H, d, J=7.3 Hz), 3.52 (1H, m), 3.93 (1H, m), 4.41 (1H, q, J=7.0 Hz), 4.89 (1H, s), 6.47 (1H, d, J=16.5 Hz), 7.08-7.15 (2H, m), 7.34-7.40 (2H, m), 7.37 (2H, d, J=8.3 Hz), 7.44 (1H, d, J=16.5 Hz), 7.52 (2H, d, J=8.0 Hz);
MASS (ES+): m/e 392 (M+1).

Preparation 152

Compound (152) was obtained according to a manner similar to Preparation 6 (1.2 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.51 (3H, d, J=6.9 Hz), 1.53 (9H, s), 3.76 (1H, q, J=7.1 Hz), 6.34 (1H, d, J=16.0 Hz), 7.33 (2H, d, J=8.5 Hz), 7.47 (2H, d, J=81 Hz), 7.56 (1H, d, J=16.0 Hz);
MASS (ES+): not detected.

Preparation 153

Compound (153) was obtained from Compound (152) according to a manner similar to Preparation 7 (1.298 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (9H, s), 1.61 (3H, d, J=7.0 Hz), 3.79 (1H, q, J=7.0 Hz), 6.36 (1H, d, J=16.0 Hz), 6.70-6.75 (2H, m), 6.97-7.05 (1H, m), 7.09-7.14 (1H, m), 7.24 (2H, d, J=8.4 Hz), 7.51 (2H, d, J=8.5 Hz), 7.56 (1H, d, J=16.2 Hz);
MASS (ES+): m/e 367 (M+1).

Preparation 154

Compound (154) was obtained from Compound (153) according to a manner similar to Preparation 8 (611 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.86 (3H, d, J=7.4 Hz), 4.83 (1H, q, J=7.1 Hz), 6.55 (1H, d, J=15.7 Hz), 7.49 (2H, d, J=8.0 Hz), 7.52-7.55 (2H, m), 7.58 (1H, d, J=16.2 Hz), 7.74 (2H, d, J=8.4 Hz), 7.76-7.79 (2H, m);
MASS (ES+): m/e 293 (M+1).

Preparation 155

Compound (155) was obtained from Compound (154) according to

a manner similar to Preparation 9 (700 mg). The Compound (155) was used in Example 47.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.52 (3H, br), 1.68 (3H, br), 1.70 (3H, d, J=6.9 Hz), 3.50 (1H, m), 3.93 (1H, m), 4.41 (1H, q, J=7.1 Hz), 4.89 (1H, s), 6.48 (1H, d, J=16.1 Hz), 7.08-7.14 (2H, m), 7.34-7.40 (2H, m), 7.37 (2H, d, J=8.3 Hz), 7.47 (2H, d, J=16.1 Hz), 7.51 (2H, d, J=8.9 Hz);

MASS (ES+): m/e 392 (M+1).

Preparation 156

Compound (156) was obtained according to a manner similar to Preparation 7 (536 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.34 (3H, t, J=7.0 Hz), 1.46 (9H, s), 1.48 (9H, s), 4.05 (2H, q, J=7.0 Hz), 6.50 (1H, d, J=16.1 Hz), 6.98 (2H, d, J=8.4 Hz), 7.01 (1H, d, J=7.7 Hz), 7.40 (2H, d, J=7.7 Hz), 7.50 (2H, d, J=8.8 Hz), 7.52 (1H, d, J=8.4 Hz), 7.55 (1H, d, J=16.3 Hz), 7.66 (2H, d, J=8.1 Hz), 7.68 (1H, s);

MASS (ES+): m/e 573 (M+1).

Preparation 157

Compound (157) was obtained from Compound (156) according to a manner similar to Preparation 8 (345 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.36 (3H, t, J=7.0 Hz), 4.08 (2H, q, J=7.0 Hz), 4.55 (2H, s), 6.56 (1H, d, J=16.1 Hz), 7.05 (2H, d, J=8.8 Hz), 7.49 (2H, d, J=8.4 Hz), 7.60 (1H, d, J=16.1 Hz), 7.65 (2H, d, J=9.1 Hz), 7.74 (2H, d, J=8.4 Hz), 7.77 (2H, m), 7.88 (1H, s);

MASS (ES+): m/e 399 (M+1).

Preparation 158

Compound (158) was obtained from Compound (157) according to a manner similar to Preparation 9 (370 mg). The Compound (158) was used in Example 48.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.35 (3H, t, J=7.0 Hz), 1.54 (3H, br), 1.68 (3H, br), 3.53 (1H, m), 3.94 (1H, m), 4.06 (2H, q, J=7.0 Hz), 4.21 (2H, s), 4.90 (1H, s), 6.48 (1H, d, J=16.1 Hz), 7.00 (2H, dd, J=8.8,2.2 Hz), 7.38 (3H, m), 7.44 (1H, s), 7.50 (1H, m), 7.53-7.60 (5H, m), 7.72 (1H, s);

MASS (ES+): m/e 498 (M+1).

Preparation 159

Compound (159) was obtained from Compound (6) according to a

manner similar to Preparation 7 (652 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.47 (9H, s), 1.49 (9H, s), 3.77 (2H, s), 6.50 (1H, d, J=16.1 Hz), 7.40 (2H, d, J=7.9 Hz), 7.49 (1H, d, J=7.9 Hz), 7.50 (1H, m), 7.60 (1H, m), 7.67 (2H, d, J=8.1 Hz), 8.00 (1H, m), 8.51 (1H, m), 8.55 (1H, m), 8.83 (1H, m), 9.76 (1H, d, J=7.7 Hz);

MASS (ES+): m/e 530 (M+1).

Preparation 160

Compound (160) was obtained from Compound (159) according to a manner similar to Preparation 8 (458 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.56 (1H, d, J=16.1 Hz), 7.51 (2H, d, J=8.1 Hz), 7.59 (1H, d, J=16.1 Hz), 7.74 (2H, d, J=8.4 Hz), 7.90 (2H, s), 8.14 (1H, s), 8.53 (1H, d, J=7.7 Hz), 8.76 (1H, d, J=5.1 Hz), 9.15 (1H, s);

MASS (ES+): m/e 356 (M+1).

Preparation 161

Compound (161) was obtained from Compound (160) according to a manner similar to Preparation 9 (316 mg). The Compound (161) was used in Example 49.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.69 (3H, br), 3.53 (1H, m), 3.95 (1H, m), 4.23 (2H, s), 4.90 (1H, s), 6.48 (1H, d, J=15.7 Hz), 7.39 (2H, d, J=8.1 Hz), 7.44-7.52 (4H, m), 7.54 (2H, d, J=8.4 Hz), 7.80 (1H, br), 8.08 (1H, m), 8.53 (1H, m), 8.90 (1H, m);

MASS (ES+): m/e 455 (M+1).

Preparation 162

Compound (162) was obtained according to a manner similar to Preparation 7 (748 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (9H, s), 3.80 (2H, s), 6.38 (1H, d, J=16.1 Hz), 6.76 (1H, d, J=8.1 Hz), 7.11 (sH,), 7.38 (2H, d, J=7.7 Hz), 7.47 (2H, d, J=7.7 Hz), 7.52-7.60 (5H, m), 7.71 (2H, d, J=7.0 Hz);

MASS (ES+): m/e 457 (M+1).

Preparation 163

Compound (163) was obtained from Compound (162) according to a manner similar to Preparation 8 (521 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.49 (2H, s), 6.54 (1H, d, J=16.1 Hz), 7.47 (2H, d, J=7.7 Hz), 7.56-7.62 (3H, m), 7.67-7.77 (3H, m), 7.81 (2H, s), 7.98 (1H, s);

MASS (ES+): m/e 383 (M+1).

Preparation 164

Compound (164) was obtained from Compound (163) according to a manner similar to Preparation 9 (185 mg). The Compound (164) was used in Example 50.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.69 (3H, br), 3.53 (1H, m), 3.95 (1H, m), 4.27 (2H, s), 4.90 (1H, s), 6.48 (1H, d, J=16.1 Hz), 7.39 (2H, d, J=8.0 Hz), 7.46 (1H, d, J=15.7 Hz), 7.56 (5H, m), 7.62 (2H, s), 7.67 (3H, m), 7.73 (2H, d, J=7.0 Hz), 7.86 (1H, s);

MASS (ES+): m/e 482 (M+1).

Preparation 165

To a solution of Compound (60) in EtOH (3 mL) was added sodium borohydride (28 mg) at 5°C and the mixture was allowed to warm to ambient temperature. After stirred for 0.5 hr, sodium borohydride (14 mg) was added to the mixture, and sodium borohydride (14 mg) was then additionally added three times to the mixture before Compound (60) was disappeared. The mixture was poured into water and washed with ether. The aqueous phase was acidified with 1N hydrochloric acid to pH 4 and extracted with ethyl acetate, washed with brine. The organic phase was dried over Na_2SO_4 and the soluvent was removed in vacuo to give Compound (165) (120 mg) as colorless form.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.44 (2H, s), 5.86 (1H, s), 6.06 (1H, br), 6.53 (1H, d, J=16.1 Hz), 7.19 (1H, t, J=7.3 Hz), 7.29 (2H, t, J=7.3 Hz), 7.38 (3H, d, J=7.0 Hz), 7.42 (2H, d, J=8.1 Hz), 7.56 (1H, d, J=5.5 Hz), 7.60 (1H, d, J=1.8 Hz), 7.67 (1H, s), 7.70 (2H, d, J=8.4 Hz);

MASS (ES+): m/e 385 (M+1).

Preparation 166

Compound (166) was obtained from Compound (165) according to a manner similar to Preparation 9 (104 mg). The Compound (166) was used in Example 51.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.68 (3H, br), 3.50 (1H, m), 3.93 (1H, m), 4.16 (2H, s), 4.90 (1H, s), 5.77 (1H, s), 5.82 (1H, br), 6.45 (1H, d, J=16.5 Hz), 7.12 (1H, m), 7.18 (1H, d, J=6.6 Hz), 7.27 (2H, d, J=7.5 Hz), 7.32 (2H, t, J=7.3 Hz), 7.34 (1H, s), 7.36 (2H, d, J=7.4 Hz), 7.42 (2H, m), 7.51 (2H, d, J=8.1 Hz);

MASS (ES+): m/e 484 (M+1).

Preparation 167

Compound (167) was obtained from Compound (6) according to a manner similar to Preparation 7 (234 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 2.96 (3H, s), 2.98 (3H, s), 3.80 (2H, s), 6.38 (1H, d, J=16.8 Hz), 6.75 (2H, d, J=8.5 Hz), 6.95 (1H, s), 6.99 (1H, d, J=7.3 Hz), 7.14 (1H, d, J=7.3 Hz), 7.40 (2H, d, J=7.0 Hz), 7.43 (2H, d, J=7.0 Hz), 7.54 (2H, d, J=7.3 Hz), 7.59 (1H, d, J=15.0 Hz);

MASS (ES+): m/e 472 (M+1).

Preparation 168

Compound (168) was obtained from Compound (167) according to a manner similar to Preparation 8 (263 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.04 (6H, s), 4.60 (2H, s), 6.57 (1H, d, J=16.1 Hz), 7.42 (1H, d, J=8.1 Hz), 7.60 (1H, d, J=16.1 Hz), 7.61-7.72 (2H, m), 7.74 (2H, d, J=8.4 Hz), 7.80 (2H, s), 7.90 (1H, s);

MASS (ES+): m/e 398 (M+1).

Preparation 169

Compound (169) was obtained from Compound (168) according to a manner similar to Preparation 9 (116 mg). The Compound (169) was used in Example 52.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.54 (3H, br), 1.69 (3H, br), 2.93 (6H, s), 3.53 (1H, m), 3.94 (1H, m), 4.20 (2H, s), 4.90 (1H, s), 6.47 (1H, d, J=15.8 Hz), 6.81 (2H, d, J=9.1 Hz), 7.38 (4H, d, J=8.4 Hz), 7.43 (1H, m), 7.50 (2H, m), 7.54 (2H, d, J=8.4 Hz), 7.69 (1H, s);

MASS (ES+): m/e 497 (M+1).

Preparation 170

Compound (170) was obtained from Compound (6) according to a manner similar to Preparation 7 (334 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.54 (9H, s), 3.81 (2H, s), 4.02 (2H, br), 6.39 (1H, d, J=16.1 Hz), 7.03 (1H, br), 7.29 (1H, br), 7.38 (2H, d, J=8.0 Hz), 7.44 (1H, br), 7.55 (2H, dd, J=8.0 Hz), 7.58 (1H, d, J=16.2 Hz);

MASS (ES+): m/e 421 (M+1).

Preparation 171

Compound (171) was obtained from Compound (170) according to a manner similar to Preparation 8 (247 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.39 (2H, s), 6.52 (1H, d, J=15.6 Hz),

7.42 (2H, d, J=7.7 Hz), 7.58 (1H, d, J=15.8 Hz), 7.61 (1H, d, J=8.8 Hz), 7.69 (2H, d, J=8.1 Hz), 7.79 (1H, d, J=9.5 Hz), 7.97 (1H, s);
MASS (ES+): m/e 347 (M+1).

Preparation 172

Compound (172) was obtained from Compound (171) according to a manner similar to Preparation 9 (308 mg). The Compound (172) was used in Example 53.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.76 (3H, br), 3.52 (1H, m), 3.96 (1H, m), 4.27 (2H, s), 4.90 (1H, s), 6.48 (1H, d, J=16.4 Hz), 7.38 (2H, d, J=8.5 Hz), 7.46 (1H, d, J=8.4 Hz), 7.47 (1H, d, J=16.0 Hz), 7.55 (2H, d, J=7.9 Hz), 7.69 (1H, d, J=8.1 Hz), 7.85 (1H, s);
MASS (ES+): m/e 346 (M+1).

Preparation 173

Compound (173) was obtained from Compound (6) according to a manner similar to Preparation 7 (617 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.48 (9H, s), 3.69 (2H, s), 5.25 (2H, br), 6.50 (1H, d, J=15.7 Hz), 6.49-6.55 (1H, m), 6.95-7.00 (1H, m), 7.37 (2H, d, J=8.1 Hz), 7.54 (1H, d, J=16.1 Hz), 7.65 (2H, d, J=8.4 Hz);
MASS (ES+): m/e 389 (M+1).

Preparation 174

Compound (174) was obtained from Compound (173) according to a manner similar to Preparation 8 (466 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.36 (2H, s), 6.52 (1H, d, J=16.1 Hz), 7.31-7.40 (2H, m), 7.43 (2H, d, J=8.1 Hz), 7.57 (1H, d, J=15.7 Hz), 7.69 (2H, d, J=8.1 Hz);
MASS (ES+): m/e 315 (M+1).

Preparation 175

Compound (175) was obtained from Compound (174) according to a manner similar to Preparation 9 (542 mg). The Compound (175) was used in Example 54.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.69 (3H, br), 3.52 (1H, m), 3.96 (1H, m), 4.22 (2H, s), 4.90 (1H, s), 6.47 (1H, d, J=16.1 Hz), 7.13-7.22 (2H, m), 7.37 (2H, d, J=8.0 Hz), 7.47 (1H, d, J=15.7 Hz), 7.54 (2H, d, J=8.0 Hz);
MASS (ES+): m/e 414 (M+1).

Preparation 176

Compound (176) was obtained from Compound (6) according to a manner similar to Preparation 7 (555 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.93 (6H, d, J=6.6 Hz), 1.54 (9H, s), 1.62 (2H, dt, J=7.0,7.0 Hz), 1.79 (1H, hept, J=6.8 Hz), 3.76 (2H, s), 3.90 (2H, t, J=6.5 Hz), 6.30 (2H, m), 6.38 (1H, d, J=16.1 Hz), 6.91 (1H, d, J=9.5 Hz), 7.53 (2H, d, J=8.7 Hz), 7.55 (1H, d, J=16.6 Hz);

MASS (ES+): m/e 439 (M+1).

Preparation 177

Compound (177) was obtained from Compound (176) according to a manner similar to Preparation 8 (398 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.94 (6H, d, J=6.7 Hz), 1.64 (2H, dt, J=6.7,6.7 Hz), 1.79 (1H, hept, J=6.7 Hz), 4.07 (2H, t, J=6.7 Hz), 4.50 (2H, s), 6.55 (1H, d, J=16.3 Hz), 7.10 (1H, dd, J=8.4,2.2 Hz), 7.21 (1H, d, J=2.2 Hz), 7.46 (2H, d, J=8.4 Hz), 7.59 (1H, d, J=16.1 Hz), 7.62 (1H, d, J=8.7 Hz), 7.73 (2H, d, J=8.6 Hz);

MASS (ES+): m/e 365 (M+1).

Preparation 178

Compound (178) was obtained from Compound (177) according to a manner similar to Preparation 9 (176 mg). The Compound (178) was used in Example 55.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 0.92 (6H, d, J=6.7 Hz), 1.42-1.87 (6H, m), 1.64 (2H, dt, J=6.7 Hz), 1.80 (1H, hept, J=6.7 Hz), 3.52 (1H, m), 3.94 (2H, t, J=6.7 Hz), 3.97 (1H, m), 4.11 (2H, s), 5.13 (1H, s), 6.18 (1H, br.s), 6.84 (1H, dd, J=8.8,2.5 Hz), 6.90 (4H, br.s), 7.04 (1H, br.s), 7.29 (1H, br.d), 7.45 (1H, d, J=8.8 Hz);

MASS (ES+): m/e 464 (M+1).

Preparation 179

Compound (179) was obtained from Compound (6) according to a manner similar to Preparation 7 (414 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.28 (6H, d, J=6.3 Hz), 3.76 (2H, s), 4.44 (1H, hept, J=6.3 Hz), 6.28 (2H, m), 6.37 (1H, d, J=15.8 Hz), 6.91 (1H, d, J=9.0 Hz), 7.37 (2H, d, J=8.1 Hz), 7.52 (2H, d, J=8.1 Hz), 7.57 (1H, d, J=15.7 Hz);

MASS (ES+): m/e 411 (M+1).

Preparation 180

Compound (180) was obtained from Compound (179) according to a manner similar to Preparation 8 (330 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.29 (6H, d, J=6.1 Hz), 4.69 (1H, hept, J=6.1 Hz), 6.55 (1H, d, J=16.2 Hz), 7.08 (1H, dd, J=2.6,9.2 Hz), 7.19 (1H, d, J=2.6 Hz), 7.59 (1H, d, J=16.1 Hz), 7.62 (1H, d, J=9.2 Hz), 7.73 (2H, d, J=8.2 Hz);

MASS (ES+): m/e 337 (M+1).

Preparation 181

Compound (181) was obtained from Compound (180) according to a manner similar to Preparation 9 (281 mg). The obtained Compound (181) was used in Example 56.

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 1.31 (6H, d, J=6.0 Hz), 1.53 (3H, br), 1.69 (3H, br), 3.64 (1H, m), 4.01 (1H, m), 4.22 (2H, s), 4.47 (1H, hept, J=6.0 Hz), 5.05 (1H, m), 6.30 (1H, br), 6.85 (1H, d, J=9.0 Hz), 7.00 (1H, s), 707-7.20 (2H, br), 7.26-7.35 (1H, br), 7.42 (2H, d, J=8.8 Hz);

MASS (ES+): m/e 436 (M+1).

Preparation 182

Compound (182) was obtained from Compound (6) according to a manner similar to Preparation 7 (546 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.78 (2H, s), 6.38 (1H, d, J=16.1 Hz), 6.40 (2H, m), 6.89 (1H, s), 7.00 (2H, m), 7.09 (1H, t, J=7.3 Hz), 7.31 (2H, dd, J=8.7,7.6 Hz), 7.38 (2H, d, J=8.5 Hz), 7.54 (2H, d, J=7.4 Hz), 7.58 (1H, d, J=16.2 Hz);

MASS (ES+): m/e 445 (M+1).

Preparation 183

Compound (183) was obtained from Compound (182) according to a manner similar to Preparation 8 (417 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.52 (2H, s), 6.56 (1H, d, J=16.1 Hz), 7.17 (1H, t, J=7.3 Hz), 7.21 (1H, dd, J=9.1,2.3 Hz), 7.30 (1H, d, J=2.3 Hz), 7.41 (2H, t, J=8.1 Hz), 7.48 (2H, d, J=8.5 Hz), 7.59 (1H, d, J=16.3 Hz), 7.73 (2H, d, J=8.8 Hz), 7.76 (1H, d, J=9.1 Hz);

MASS (ES+): m/e 371 (M+1).

Preparation 184

Compound (184) was obtained from Compound (183) according to a manner similar to Preparation 9 (442 mg). The Compound (184) was used in Example 57.

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.54 (3H, br), 1.69 (3H, br), 3.52 (1H, m), 3.95 (1H, m), 4.19 (2H, s), 4.90 (1H, s), 6.47 (1H, d, J=16.5 Hz), 6.88 (1H, m), 6.94 (2H, m), 7.06 (2H, m), 7.35 (2H, m), 7.37

(3H, m), 7.46 (1H, d, J=16.4 Hz), 7.54 (2H, m);
MASS (ES+): m/e 470 (M+1).

Preparation 185

Compound (185) was obtained from Compound (6) according to a manner similar to Preparation 7 (163 mg).
^{1}H-NMR (300 MHz, $CDCl_3$, δ): 3.74 (3H, s), 3.78 (2H, s), 6.31 (2H, m), 6.38 (1H, d, J=16.1 Hz), 6.93 (1H, d, J=10.0 Hz), 7.38 (2H, d, J=8.0 Hz), 7.54 (2H, d, J=8.4 Hz), 7.58 (1H, d, J=16.1 Hz);
MASS (ES+): m/e 383 (M+1).

Preparation 186

Compound (186) was obtained from Compound (185) according to a manner similar to Preparation 8 (127 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.84 (3H, s), 4.52 (2H, s), 6.55 (1H, d, J=16.1 Hz), 7.12 (1H, dd, J=8.8,2.2 Hz), 7.20 (1H, d, J=2.6 Hz), 7.47 (2H, d, J=8.1 Hz), 7.59 (1H, d, J=16.1 Hz), 7.65 (1H, d, J=9.2 Hz), 7.73 (2H, d, J=8.1 Hz);
MASS (ES+): m/e 309 (M+1).

Preparation 187

Compound (187) was obtained from Compound (186) according to a manner similar to Preparation 9 (127 mg). The Compound (187) was used in Example 58.
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.53 (3H, br), 1.69 (3H, br), 3.53 (1H, m), 3.75 (3H, s), 3.95 (1H, m), 4.15 (2H, s), 6.48 (1H, d, J=15.7 Hz), 6.75 (1H, dd, J=8.8,2.6 Hz), 6.98 (1H, s), 7.35 (3H, d, J=8.4 Hz), 7.46 (1H, d, J=15.7 Hz), 7.53 (2H, d, J=8.0 Hz);
MASS (ES+): m/e 408 (M+1).

Example 1

To a stirred solution of Compound (5) (125 mg) in methanol (5 mL) was added hydrogen chloride methanol reagent 10 (0.5 mL, manufactured by Tokyo Kasei Kogyo Co., Ltd.), and the mixture was stirred at ambient temperature for 30 minutes. The solvent was evaporated in vacuo and the residue was triturated with the mixture of methanol and ethyl acetate (1:2) to give Compound E1 as a white solid (81 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.57 (2H, s), 6.50 (1H, d, J=15.7 Hz), 7.41-7.56 (5H, m), 7.60 (2x1H, d, J=8 Hz), 7.73-7.81 (2H, m), 10.84 (1H, br);
MASS (ES+): m/e 294.

Example 2

Compound E2 was obtained from Compound (13) according to a manner similar to Example 1 (79 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.76 (2H, s), 5.82 (2H, s), 6.49 (1H, d, J=16 Hz), 7.12-7.21 (2H, m), 7.26-7.34 (3H, m), 7.38-7.62 (7H, m), 7.73 (1H, dd, J=7, 1.5 Hz), 7.83 (1H, dd, J=7, 1.5 Hz);

MASS (ES+): m/e 384.

Example 3

Compound E3 was obtained from Compound (19) according to a manner similar to Example 1 (1.74 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.28 (2x1H, t, J=7.5 Hz), 3.47 (2x1H, t, J=7.5 Hz), 6.45 (1H, d, J=16 Hz), 7.32 (2x1H, d, J=8 Hz), 7.41 (1H, d, J=16 Hz), 7.46-7.60 (4H, m), 7.73-7.83 (2H, m), 10.80 (1H, s), 15.10 (1H, br);

MASS (ES+): m/e 308.

Example 4

Compound E4 was obtained from Compound (22) according to a manner similar to Example 1 (377 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.79 (2H, s), 6.50 (1H, d, J=16 Hz), 7.43 (1H, d, J=16 Hz), 7.48-7.64 (6H, m), 7.86-7.94 (2H, m), 9.84 (1H, s);

MASS (ES+): m/e 294.

Example 5

Compound E5 was obtained from Compound (25) according to a manner similar to Example 1 (102 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.31 (1H, m), 3.70 (1H, dd, J=13, 8 Hz), 4.74 (1H, br-t, J=8 Hz), 5.34 (1H, d, J=17 Hz), 5.41 (1H, d, J=17 Hz), 6.37 (1H, d, J=15.5 Hz), 6.73 (2x1H, d, J=6.5 Hz), 7.07-7.45 (16H, m), 7.71 (1H, d, J=7.5 Hz), 9.02 (1H, brs), 10.73 (1H, brs);

MASS (ES+): m/e 474.

Example 6

Compound E6 was obtained from Compound (29) according to a manner similar to Example 1 (1.88 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.57 (2H, s), 6.51 (1H, d, J=16 Hz), 7.40-7.56 (6H, m), 7.68 (1H, s), 7.73-7.81 (2H, m), 10.88 (1H, s);

MASS (ES+): m/e 294.

Example 7

Compound E7 was obtained from Compound (32) according to a manner similar to Example 1 (162 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.50 (1H, d, J=15.7 Hz), 7.38-7.56 (6H, m), 7.61 (2x1H, d, J=8 Hz), 7.73 (2x1H, d, J=7 Hz), 7.78-7.88 (2H, m), 7.96 (1H, s), 10.84 (1H, s);

MASS (ES+): m/e 370.

Example 8

Compound E8 was obtained from Compound (34) according to a manner similar to Example 1 (75 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.50 (2H, s), 6.48 (1H, d, J = 16 Hz), 7.42-7.48 (3H, m), 7.56-7.71 (4H, m), 7.97 (1H, d, J = 2 Hz);

MASS (ESI): m/z 372 (M+1).

Example 9

Compound E9 was obtained from Compound (35) according to manners similar to Preparation 9 and Example 1 (152 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.63 (3H, s), 4.58 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.46 (1H, d, J = 16 Hz), 7.50 (2H, d, J = 8 Hz), 7.61 (2H, d, J = 8 Hz), 7.85-7.93 (4H, m), 8.04-8.10 (3H, m);

MASS (ESI): m/z 412 (M+1).

Example 10

Compound E10 was obtained from Compound (36) according to manners similar to Preparation 9 and Example 1 (138 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.50 (1H, d, J = 16 Hz), 7.17-7.21 (1H, m), 7.46 (1H, d, J = 16 Hz), 7.51 (2H, d, J = 8 Hz), 7.59-7.65 (4H, m), 7.80-7.83 (2H, m), 7.95 (1H, s);

MASS (ESI): m/z 376 (M+1).

Example 11

Compound E11 was obtained from Compound (37) according to manners similar to Preparation 9 and Example 1 (120 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.46 (1H, d, J = 16 Hz), 7.51 (2H, d, J = 8 Hz), 7.61 (2H, d, J = 8 Hz), 7.64-7.73 (2H, m), 7.79 (1H, d, J = 8 Hz), 7.90 (1H, dd, J = 2, 8 Hz), 8.00-8.05 (2H, m);

MASS (ESI): m/z 376 (M+1).

Example 12

Compound E12 was obtained from Compound (39) according to a manner similar to Example 1 (142 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.42 (2H, s), 6.46 (1H, d, J = 16 Hz),

7.41-7.47 (3H, m), 7.56 (2H, d, J = 8 Hz), 7.73 (1H, d, J = 8 Hz), 7.80 (1H, d, J = 8 Hz), 8.22 (1H, s);
MASS (ESI): m/z 317 (M-1).

Example 13

Compound E13 was obtained from Compound (40) according to manners similar to Preparation 9 and Example 1 (710 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.55 (2H, s), 6.50 (1H, d, J = 16 Hz), 7.36-7.44 (1H, m), 7.45 (1H, d, J = 16 Hz), 7.50 (2H, d, J = 8 Hz), 7.59 (2H, d, J = 8 Hz), 7.66 (1H, dd, J = 2, 8 Hz), 7.77-7.83 (1H, m);
MASS (ESI): m/z 312 (M+1).

Example 14

Compound E14 was obtained from Compound (42) according to a manner similar to Example 1 (504 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.51 (2H, s), 6.48 (1H, d, J = 16 Hz), 7.45 (1H, d, J = 16 Hz), 7.47 (2H, d, J = 8 Hz), 7.52 (1H, dd, J = 2, 8 Hz), 7.59 (2H, d, J = 8 Hz), 7.76 (1H, d, J = 8 Hz), 7.86 (1H, J = 2 Hz);
MASS (ESI): m/z 328 (M+1).

Example 15

Compound E15 was obtained from Compound (44) according to a manner similar to Example 1 (14 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.79-2.85 (4H, m), 3.11-3.22 (4H, m), 4.52 (2H, s), 6.48 (1H, d, J = 16 Hz), 7.15-7.67 (8H, m);
MASS (ESI): m/z 392 (M+1).

Example 16

Compound E16 was obtained from Compound (46) according to a manner similar to Example 1 (45 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.15-3.21 (4H, m), 3.75-3.81 (4H, m), 4.52 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.10 (1H, d, J = 2 Hz), 7.29 (1H, dd, J = 2, 8 Hz), 7.42-7.50 (3H, m), 7.57-7.64 (3H, m);
MASS (ESI): m/z 379 (M+1).

Example 17

Compound E17 was obtained from Compound (48) according to a manner similar to Example 1 (27 mg).
^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.60-1.70 (2H, m), 1.83-2.00 (4H, m), 3.39-3.54 (4H, m), 4.54 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.40-7.86 (8H, m);

MASS (ESI): m/z 377 (M+1).

Example 18

A mixture of Compound (39), sodium azide (485 mg) and triethylamine hydrochloride (1.54 g) in N,N-dimethylformamide (7.5 mL) was heated at 130°C for 6 hours. After cooling, the reaction mixture was partitioned between ethyl acetate (20 mL) and water (40 mL). The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated in vacuo. The crude product was triturated with ethyl acetate-water. The product was treated according to a manner similar to Example 1 to give Compound E18 (18 mg):

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.30 (2H, s), 6.44 (1H, d, J = 16 Hz), 7.40 (2H, d, J = 8 Hz), 7.44 (1H, d, J = 16 Hz), 7.55 (2H, d, J = 8 Hz), 7.72 (1H, d, J = 8 Hz), 7.90 (1H, d, J = 8 Hz), 8.21 (1H, s);
MASS (ESI): m/z 362 (M+1).

Example 19

Compound E19 was obtained from Compound (50) according to a manner similar to Example 1 (101 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.91 (3H, s), 4.55 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.46 (1H, d, J = 16 Hz), 7.50 (2H, d, J = 8 Hz), 7.60 (2H, d, J = 8 Hz), 7.84 (1H, d, J = 8 Hz), 8.05 (1H, d, J = 8 Hz), 8.27 (1H, s);
MASS (ESI): m/z 352 (M+1).

Example 20

Compound E20 was obtained from Compound (51) according to a manner similar to Example 1 (72 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.55 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.45 (1H, d, J = 16 Hz), 7.49 (2H, d, J = 8 Hz), 7.60 (2H, d, J = 8 Hz), 7.81 (1H, d, J = 8 Hz), 8.04 (1H, dd, J = 2, 8 Hz), 8.25 (1H, s);
MASS (ESI): m/z 338 (M+1).

Example 21

Compound E21 was obtained from Compound (53) according to a manner similar to Example 1 (55 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 2.68 (3H, s), 4.56 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.45 (1H, d, J = 16 Hz), 7.50 (2H, d, J = 8 Hz), 7.59 (2H, d, J = 8 Hz), 7.83 (1H, d, J = 8 Hz), 8.06 (1H, dd, J = 2, 8 Hz), 8.28 (1H, s);

MASS (ESI): m/z 336 (M+1).

Example 22

Compound E22 was obtained from Compound (55) according to a manner similar to Example 1 (279 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.48 (2H, s), 6.47 (1H, d, J = 16 Hz), 7.33-7.49 (4H, m), 7.57 (2H, d, J = 8 Hz), 7.65-7.72 (4H, m);

MASS (ESI): m/z 372 (M+1).

Example 23

Compound E23 was obtained from Compound (57) according to a manner similar to Example 1 (50 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.25 (3H, s), 1.27 (3H, s), 3.04-3.16 (1H, m), 4.55 (2H, s), 6.49 (1H, d, J = 16 Hz), 7.42-7.52 (4H, m), 7.56-7.62 (3H, m), 7.68 (1H, d, J = 8 Hz);

MASS (ESI): m/z 336 (M+1).

Example 24

Compound E24 was obtained from Compound (59) according to manners similar to Preparation 9 and Example 1 (249 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.42 (2H, s), 5.35 (2H, s), 6.45 (1H, d, J = 16 Hz), 7.10-7.61 (13H, m);

MASS (ESI): m/z 400 (M+1).

Example 25

Compound E25 was obtained from Compound (62) according to a manner similar to Example 1 (417 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.50 (1H, d, J=15.7 Hz), 7.38-7.56 (6H, m), 7.61 (2x1H, d, J=8 Hz), 7.73 (2x1H, d, J=7 Hz), 7.78-7.88 (2H, m), 7.96 (1H, s), 10.84 (1H, s);

MASS (ES+): m/e 370.

Example 26

Compound E26 was obtained from Compound (67) according to a manner similar to Example 1 (508 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.71 (2H, m), 1.98 (2H, m), 6.54 (1H, d, J=15.7 Hz), 7.45-7.57 (5H, m), 7.63 (2x1H, d, J=8.5 Hz), 7.66-7.74 (2H, m), 10.88 (1H, br);

MASS (ES+): m/e 370.

Example 27

Compound E27 was obtained from Compound (72) according to a manner similar to Example 1 (207 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.57 (2H, s), 6.50 (1H, d, J=15.7 Hz),

7.35 (2x1H, dd, J=8.8, 8.8 Hz), 7.46 (1H, d, J=15.7 Hz), 7.50 (2x1H, d, J=8 Hz), 7.61 (2x1H, d, J=8 Hz), 7.74-7.86 (4H, m), 7.94 (1H, s);

MASS (ES+): m/e 388.

Example 28

Compound E28 was obtained from Compound (75) according to a manner similar to Example 1 (123 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.58 (2H, s), 6.51 (1H, d, J=15.8 Hz), 7.38-7.59 (7H, m), 7.65-7.87 (5H, m), 7.96 (1H, s), 10.86 (1H, br);

MASS (ES+): m/e 370.

Example 29

Compound E29 was obtained from Compound (80) according to a manner similar to Example 1 (103 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.28 (3H, s), 4.59 (2H, s), 6.49 (1H, d, J=16 Hz), 7.42-7.65 (5H, m), 7.87-7.92 (2H, m), 7.98-8.10 (5H, m);

MASS (ES+): m/e 447.

Example 30

Compound E30 was obtained from Compound (83) according to a manner similar to Example 1 (200 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.49 (2H, s), 6.49 (1H, d, J=16 Hz), 7.44 (1H, d, J=16 Hz), 7.47 (2x1H, d, J=8 Hz), 7.57 (2x1H, d, J=8 Hz), 7.57 (1H, dd, J=8, 5 Hz), 8.34 (1H, d, J=8 Hz), 8.58 (1H, d, J=5 Hz);

MASS (ES+): m/e 295.

Example 31

Compound E31 was obtained from Compound (90) according to a manner similar to Example 1 (175 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.52 (2H, s), 6.50 (1H, d, J=16 Hz), 7.23 (1H, br-d, J=8.5 Hz), 7.41-7.53 (4H, m), 7.59 (2x1H, d, J=8 Hz), 7.69 (1H, d, J=8.5 Hz);

MASS (ES+): m/e 309.

Example 32

Compound E32 was obtained from Compound (93) according to a manner similar to Example 1 (14 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.92 (3H, t, J=7.5 Hz), 1.63 (2H, tq, J=7.5, 7.5 Hz), 2.34 (2H, t, J=7.5 Hz), 4.54 (2H, s), 6.49 (1H, d, J=15.7 Hz), 7.41-7.51 (3H, m), 7.55 (1H, dd, J=9, 2 Hz), 7.60 (2x1H,

d, J=8.5 Hz), 7.69 (1H, d, J=9 Hz), 8.31 (1H, d, J=2 Hz);
MASS (ES+): m/e 379.

Example 33

Compound E33 was obtained from Compound (97) according to a manner similar to Example 1 (73 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.45 (2H, s), 6.45 (1H, d, J=16 Hz), 7.43 (1H, d, J=16 Hz), 7.45 (2x1H, d, J=8 Hz), 7.50 (2x1H, dd, J=8, 8 Hz), 7.54 (2x1H, d, J=8 Hz), 8.11 (1H, d, J=8 Hz), 8.21 (1H, d, J=8 Hz);

MASS (ES+): m/e 339.

Example 34

Compound E34 was obtained from Compound (100) according to a manner similar to Example 1 (15 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.43 (2H, s), 6.48 (1H, d, J=16 Hz), 7.39-7.60 (5H, m), 8.08 (1H, d, J=6.5 Hz), 8.55 (1H, d, J=6.5 Hz), 9.35 (1H, s);

MASS (ES+): m/e 295.

Example 35

Compound E35 was obtained from Compound (103) according to a manner similar to Example 1 (240 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.22 (3H, s), 3.40 (3H, s), 4.08 (2H, s), 6.44 (1H, d, J=15.8 Hz), 7.32 (2x1H, d, J=8 Hz), 7.42 (1H, d, J=15.8 Hz), 7.51 (2x1H, d, J=8 Hz);

MASS (ES+): m/e 356.

Example 36

Compound E36 was obtained from Compound (105) according to a manner similar to Example 1 (160 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.42 (2H, s), 6.47 (1H, d, J=16 Hz), 7.44 (1H, d, J=16 Hz), 7.44 (2x1H, d, J=8 Hz), 7.56 (2x1H, d, J=8 Hz), 7.80 (1H, d, J=9 Hz), 8.19 (1H, dd, J=9, 2.2 Hz), 8.50 (1H, d, J=2.2 Hz);

MASS (ES+): m/e 339.

Example 37

Compound E37 was obtained from Compound (112) according to a manner similar to Example 1 (375 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ): 5.66 (2H, s), 6.38 (1H, d, J=15.7 Hz), 7.19 (2x1H, d, J=8.8 Hz), 7.43 (1H, d, J=15.7 Hz), 7.48-7.56 (2H, m), 7.58 (2x1H, d, J=8.8 Hz), 7.76-7.84 (2H, m), 10.75 (1H, br-s);

MASS (ES+): m/e 310.

Example 38

Compound E38 was obtained from Compound (115) according to a manner similar to Example 1 (40 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.40-1.94 (8H, m), 3.85 (1H, m), 4.54 (2H, s), 6.51 (1H, d, J=15.8 Hz), 7.28-7.80 (8H, m);

MASS (ES+): m/e 377.

Example 39

Compound E39 was obtained from Compound (122) according to a manner similar to Example 1 (1.19 g).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 5.67 (2H, s), 6.53 (1H, d, J=16 Hz), 7.14 (1H, m), 7.27 (1H, m), 7.35 (1H, s), 7.41 (1H, dd, J=8, 8 Hz), 7.46 (1H, d, J=16 Hz), 7.47-7.79 (2H, m), 7.77-7.87 (2H, m),10.90 (1H, br);

MASS (ES+): m/e 310.

Example 40

Compound E40 was obtained from Compound (125) according to a manner similar to Example 1 (110 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.05 (2x3H, t, J=7 Hz), 3.52 (4H, m), 4.51 (2H, s), 6.49 (1H, d, J=15.8 Hz), 7.41-7.53 (5H, m), 7.56-7.64 (3H, m);

MASS (ES+): m/e 365.

Example 41

Compound E41 was obtained from Compound (132) according to a manner similar to Example 1 (1472 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.84 (3H, s), 5.62 (2H, s), 6.43 (1H, d, J=15.8 Hz), 7.14 (1H, d, J=8 Hz), 7.21 (1H, d, J=8 Hz), 7.28 (1H, s), 7.42 (1H, d, J=15.8 Hz), 7.50-7.58 (2H, m), 7.78-7.86 (2H, m);

MASS (ES+): m/e 340.

Example 42

Compound E42 was obtained from Compound (134) according to manners similar to Preparation 9 and Example 1 (115 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.02 (2x3H, s), 4.52 (2H, s), 6.50 (1H, d, J=16 Hz), 6.90-7.70 (8H, m);

MASS (ES+) m/e 337.

Example 43

Compound E43 was obtained from Compound (141) according to a manner similar to Example 1 (450 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.82 (3H, s), 5.61 (2H, s), 6.40 (1H, d, J=15.8 Hz), 7.11 (1H, d, J=8.8 Hz), 7.28 (1H, dd, J=8.8, 1.7 Hz), 7.40 (1H, d, J=15.8 Hz), 7.43 (1H, d, J=1.7 Hz), 7.50-7.58 (2H, m), 7.78-7.86 (2H, m);

MASS (ES+): m/e 340.

Example 44

Compound E44 was obtained from Compound (144) according to a manner similar to Example 1 (160.8 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.45 (2H, s), 6.16 (2H, s), 6.47 (1H, d, J=15.8 Hz), 7.43 (1H, d, J=8.1 Hz), 7.46 (1H, d, J=16.0 Hz), 7.59 (2H, d, J=8.1 Hz);

MASS (ES+): m/e 338 (M+1).

Example 45

Compound E45 was obtained from Compound (147) according to a manner similar to Example 1 (160.8 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.00 (3H, s), 4.42 (2H, s),6.44 (1H, d, J=16.2 Hz), 7.04 (1H, d, J=8.0 Hz), 7.27 (1H, d, J=8.4 Hz), 7.41 (1H, t, J=8.2 Hz), 7.42 (2H, d, J=8.0 Hz), 7.45 (1H, d, J=16.0 Hz), 7.57 (2H, d, J=8.0 Hz);

MASS (ES+): m/e 324 (M+1).

Example 46

Compound E46 was obtained from Compound (151) according to a manner similar to Example 1 (481.2 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.87 (3H, d, J=7.4 Hz), 4.85 (1H, q, J=7.4 Hz), 6.49 (1H, d, J=16.1 Hz), 7.43 (1H, d, J=15.7 Hz), 7.49-7.52 (2H, m), 7.51 (2H, d, J=8.5 Hz), 7.58 (2H, d, J=8.5 Hz), 7.74-7.77 (2H, m);

MASS (ES+): m/e 308 (M+1).

Example 47

Compound E47 was obtained from Compound (155) according to a manner similar to Example 1 (576.3 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.88 (3H, d, J=7.3 Hz), 4.83 (1H, q, J=7.4 Hz), 6.50 (1H, d, J=15.7 Hz), 7.43 (1H, d, J=15.4 Hz), 7.48-7.51 (2H, m), 7.53 (2H, d, J=8.2 Hz), 7.58 (2H, d, J=8.4 Hz), 7.74-7.77 (2H, m);

MASS (ES+): m/e 308 (M+1).

Example 48

Compound E48 was obtained from Compound (158) according to a

manner similar to Example 1 (274.9 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.36 (3H, t, J=7.0 Hz), 4.08 (2H, q, J=7.0 Hz), 4.58 (2H, s), 6.49 (1H, d, J=15.7 Hz), 7.05 (2H, d, J=8.8 Hz), 7.46 (1H, d, J=17.0 Hz), 7.50 (2H, d, J=8.4 Hz), 7.61 (2H, d, J=8.4 Hz), 7.66 (2H, d, J=8.8 Hz), 7.77 (1H, dd, J=8.8,1.5 Hz), 7.81 (1H, d, J=8.4 Hz), 7.90 (1H, s);

MASS (ES+): m/e 414 (M+1).

Example 49

Compound E49 was obtained from Compound (161) according to a manner similar to Example 1 (231.1 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.60 (2H, s), 6.49 (1H, d, J=15.8 Hz), 7.46 (1H, d, J=16.1 Hz), 7.52 (2H, d, J=8.4 Hz), 7.60 (2H, d, J=8.4 Hz), 7.93 (2H, s), 8.19 (1H, s), 8.66 (1H, d, J=9.0 Hz), 8.81 (1H, dd, J=5.5,1.5 Hz), 9.21 (1H, d, J=1.8 Hz);

MASS (ES+): m/e 371 (M+1).

Example 50

Compound E50 was obtained from Compound (164) according to a manner similar to Example 1 (130.9 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.54 (2H, s), 6.48 (1H, d, J=15.8 Hz), 7.46 (1H, d, J=15.8 Hz), 7.47 (2H, d, J=8.1 Hz), 7.58 (2H, t, J=7.0 Hz), 7.60 (2H, d, J=8.1 Hz), 7.71 (1H, t, J=7.7 Hz), 7.76 (2H, d, J=7.4 Hz), 7.83 (1H, dd, J=8.8,1.5 Hz), 7.87 (2H, d, J=8.4 Hz), 8.01 (1H, s);

MASS (ES+): m/e 398 (M+1).

Example 51

Compound E51 was obtained from Compound (166) according to a manner similar to Example 1 (69.3 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.51 (2H, s), 5.89 (1H, s), 6.46 (1H, d, J=45.8 Hz), 7.20 (1H, t, J=7.0 Hz), 7.30 (2H, t, J=7.3 Hz), 7.39 (2H, d, J=7.3 Hz), 7.46 (4H, m), 7.59 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=8.4 Hz), 7.74 (1H, s);

MASS (ES+): m/e 398 (M+1).

Example 52

Compound E52 was obtained from Compound (169) according to a manner similar to Example 1 (103.9 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.00 (6H, s), 4.57 (2H, s), 6.48 (1H, d, J=15.8 Hz), 7.47 (1H, d, J=15.0 Hz), 7.50 (1H, d, J=8.1 Hz), 7.61 (2H, d, J=8.4 Hz), 7.65 (2H, d, J=9.1 Hz), 7.79 (2H, s), 7.87

(1H, s);
MASS (ES+): m/e 413 (M+1).

Example 53

Compound E53 was obtained from Compound (172) according to a manner similar to Example 1 (203.9 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.46 (2H, s), 6.46 (1H, d, J=16.1 Hz), 7.44 (2H, d, J=8.5 Hz), 7.45 (1H, d, J=16.0 Hz), 7.57 (2H, d, J=8.5 Hz), 7.69 (1H, d, J=8.5 Hz), 7.85 (1H, d, J=7.8 Hz), 8.03 (1H, s);
MASS (ES+): m/e 361 (M+1).

Example 54

Compound E54 was obtained from Compound (175) according to a manner similar to Example 1 (419.6 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.35 (2H, s), 6.46 (1H, d, J=15.7 Hz), 7.31-7.40 (2H, m), 7.42 (2H, d, J=8.0 Hz), 7.43 (1H, d, J=16.0 Hz), 7.56 (2H, d, J=8.0 Hz);
MASS (ES+): m/e 330 (M+1).

Example 55

Compound E55 was obtained from Compound (178) according to a manner similar to Example 1 (90.7 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 0.94 (6H, d, J=6.6 Hz), 1.64 (2H, dt, J=6.6,6.6 Hz), 1.80 (1H, hept, J=6.6 Hz), 4.07 (2H, t, J=6.6 Hz), 4.51 (2H, s), 6.48 (1H, d, J=16.2 Hz), 7.11 (1H, dd, J=2.1,9.0 Hz), 7.21 (1H, d, J=2.1 Hz), 7.44 (2H, d, J=8.4 Hz), 7.45 (1H, d, J=16.2 Hz), 7.59 (2H, d, J=8.5 Hz), 7.63 (1H, d, J=9.0 Hz);
MASS (ES+): m/e 380 (M+1).

Example 56

Compound E56 was obtained from Compound (181) according to a manner similar to Example 1 (215.8 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 1.29 (6H, d, J=6.1 Hz), 4.51 (2H, s), 4.70 (1H, hept, J=6.1 Hz), 6.48 (1H, d, J=16.0 Hz), 7.09 (1H, dd, J=2.2, 8.9 Hz), 7.20 (1H, d, J=2.2 Hz), 7.45 (1H, d, J=16.0 Hz), 7.47 (2H, d, J=8.5 Hz), 7.59 (2H, d, J=8.1 Hz), 7.63 (1H, d, J=8.9 Hz);
MASS (ES+): m/e 352 (M+1).

Example 57

Compound E57 was obtained from Compound (184) according to a manner similar to Example 1 (387.8 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 4.52 (2H, s), 6.48 (1H, d, J=16.1 Hz),

7.04 (2H, d, J=7.7 Hz), 7.18 (1H, t, J=7.7 Hz), 7.22 (1H, dd, J=8.8,2.2 Hz), 7.30 (1H, d, J=2.2 Hz), 7.41 (2H, t, J=8.0 Hz), 7.46 (1H, d, J=16.0 Hz), 7.47 (2H, d, J=8.1 Hz), 7.57 (2H, d, J=7.7 Hz), 7.77 (1H, d, J=9.2 Hz);

MASS (ES+): m/e 386 (M+1).

Example 58

Compound E58 was obtained from Compound (187) according to a manner similar to Example 1 (78.2 mg).

^{1}H-NMR (300 MHz, DMSO-d_6, δ): 3.85 (3H, s), 4.52 (2H, s), 6.48 (1H, d, J=15.7 Hz), 7.12 (1H, dd, J=8.8, 2.2 Hz), 7.20 (1H, d, J=2.2 Hz), 7.45 (1H, d, J=15.0 Hz), 7.46 (2H, d, J=8.4 Hz), 7.60 (2H, d, J=8.4 Hz), 7.65 (1H, d, J=9.2 Hz);

MASS (ES+): m/e 324 (M+1).

The compounds obtained in the above-mentioned Preparations are shown in the following Tables 2 (including Tables 2-1 to 2-24) and the above-mentioned Examples are shown in the following Table 3 (including Tables 3-1 to 3-8).

Table 2

Table 2-1

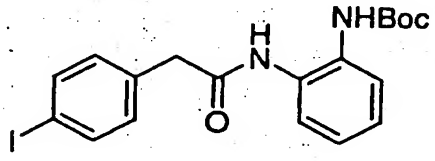
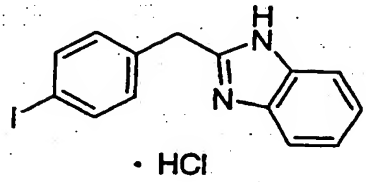
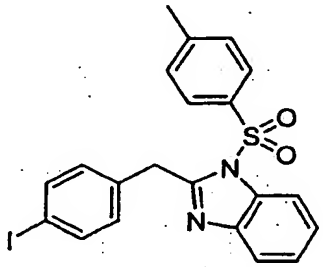
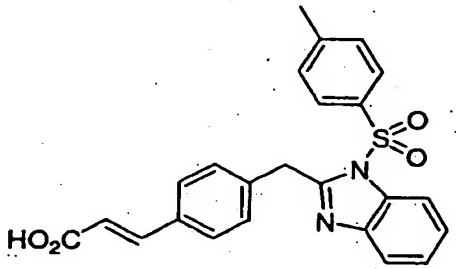
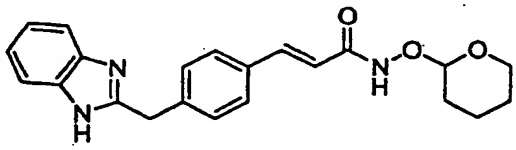
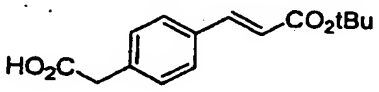
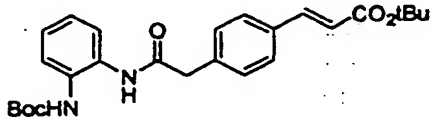
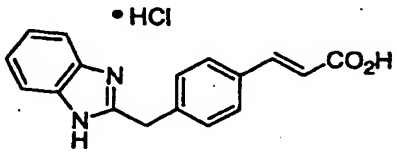
Compound (1)	Compound (2)
	
Compound (3)	**Compound (4)**
	
Compound (5)	**Compound (6)**
	
Compound (7)	**Compound (8)**
	

Table 2-2

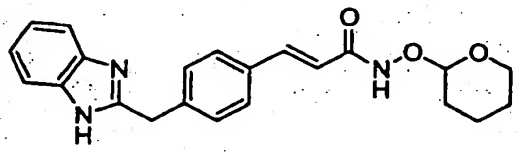
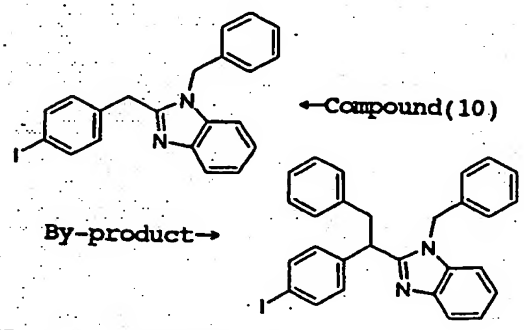
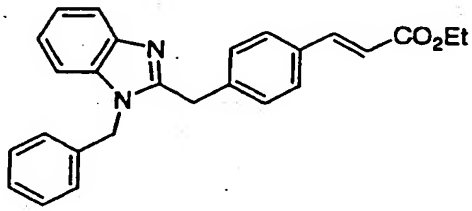
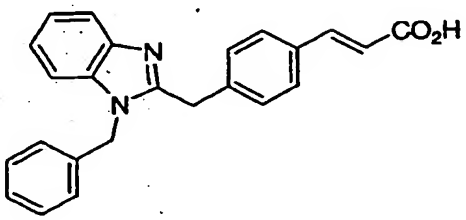
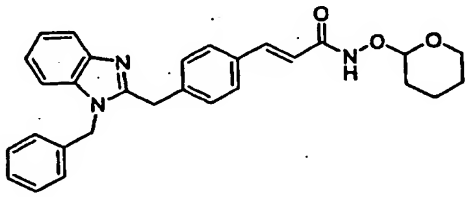
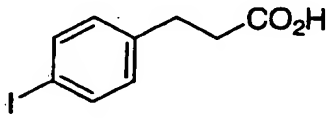
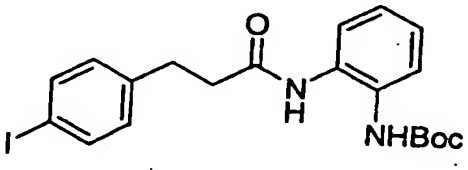
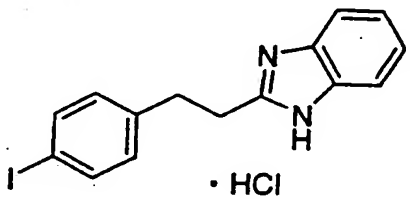
Compound (9)	Compound (10)
	
Compound (11)	**Compound (12)**
	
Compound (13)	**Compound (14)**
	
Compound (15)	**Compound (16)**
	

Table 2-3

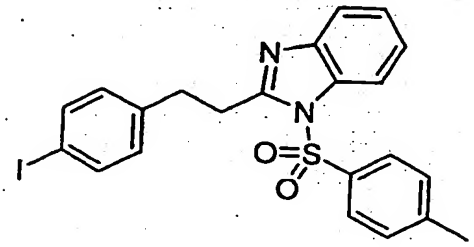
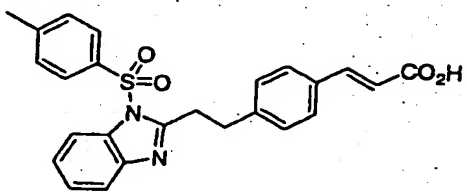
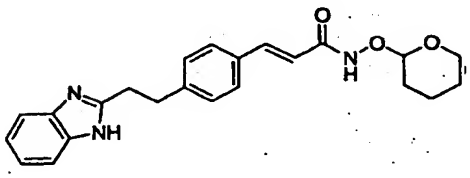
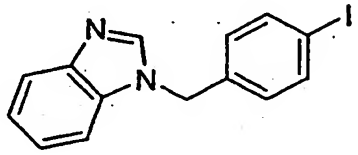
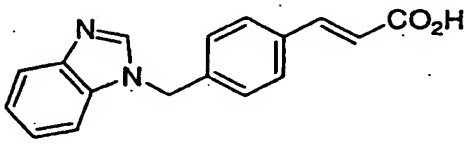
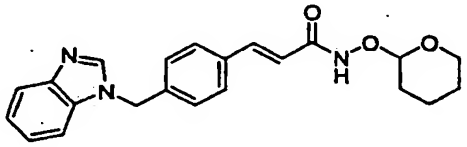
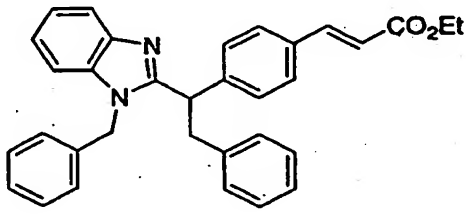
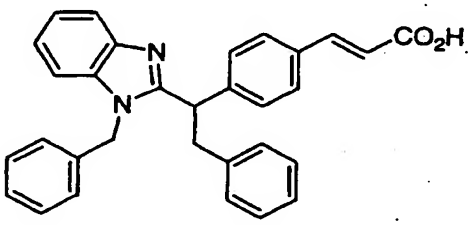
Compound (17)	Compound (18)
	
Compound (19)	**Compound (20)**
	
Compound (21)	**Compound (22)**
	
Compound (23)	**Compound (24)**
	

Table 2-4

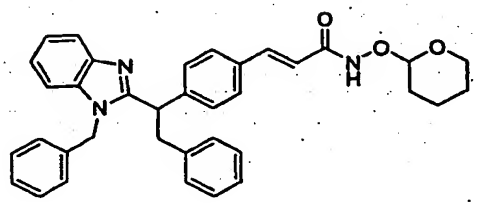
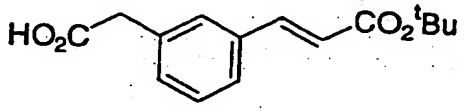
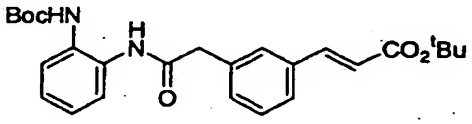
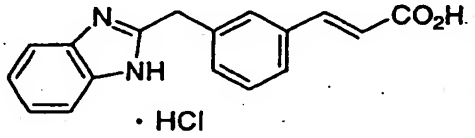
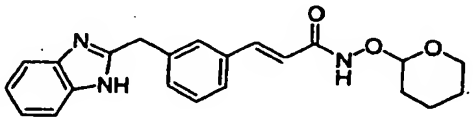
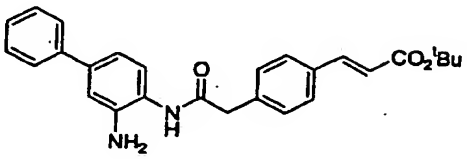
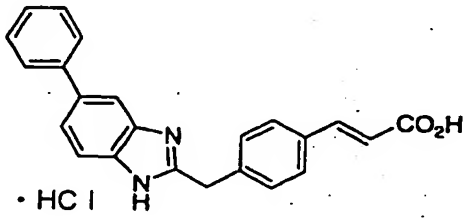
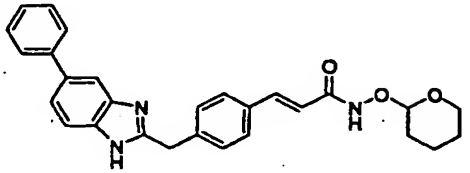
Compound (25)	Compound (26)
	
Compound (27)	**Compound (28)**
	
Compound (29)	**Compound (30)**
	
Compound (31)	**Compound (32)**
	

Table 2-5

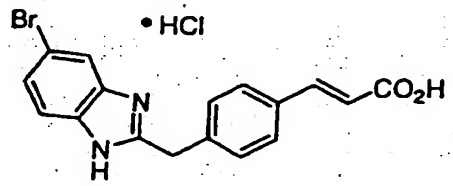
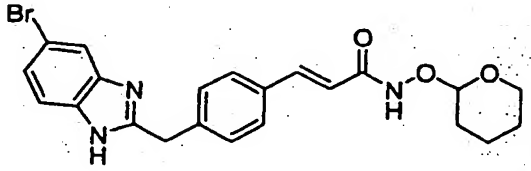
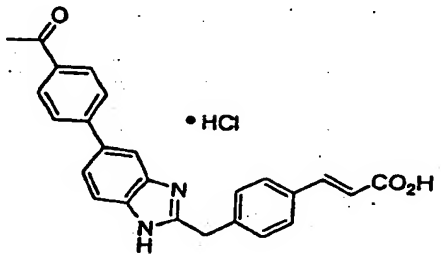
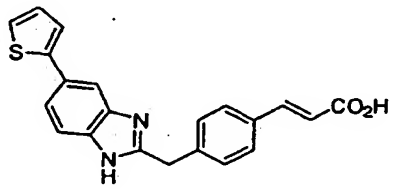
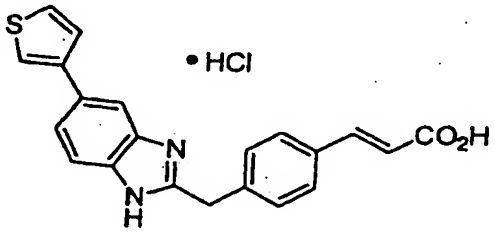
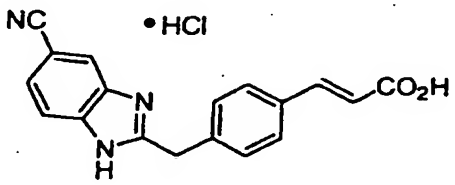
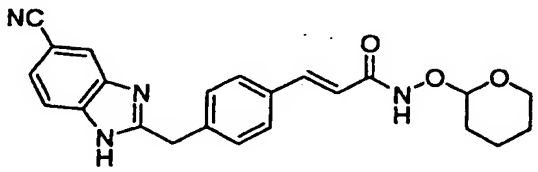
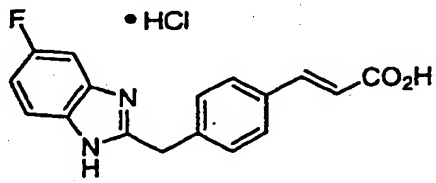
Compound (33)	Compound (34)
	
Compound (35)	**Compound (36)**
	
Compound (37)	**Compound (38)**
	
Compound (39)	**Compound (40)**
	

Table 2-6

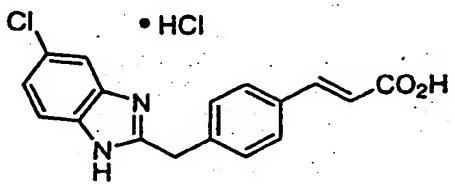
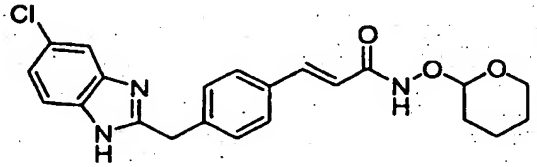
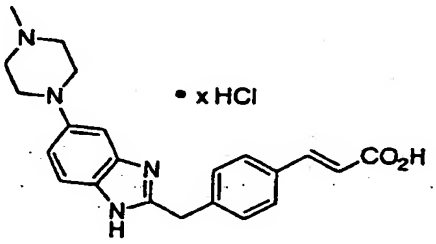
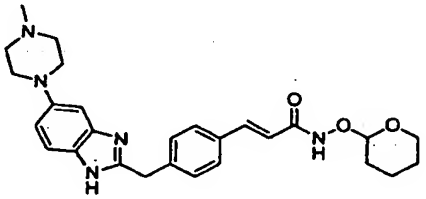
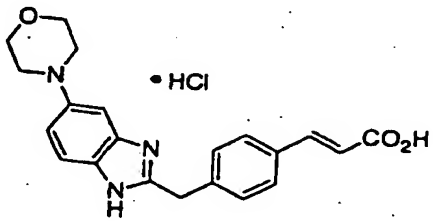
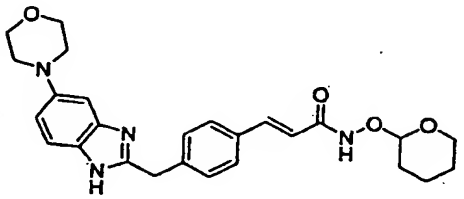
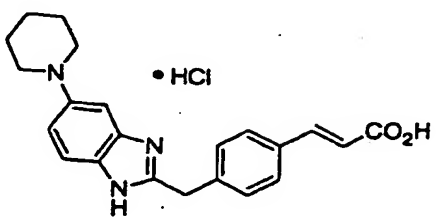
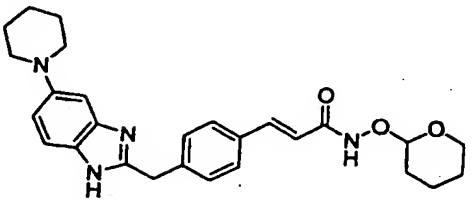
Compound (41)	Compound (42)
	
Compound (43)	**Compound (44)**
	
Compound (45)	**Compound (46)**
	
Compound (47)	**Compound (48)**
	

Table 2-7

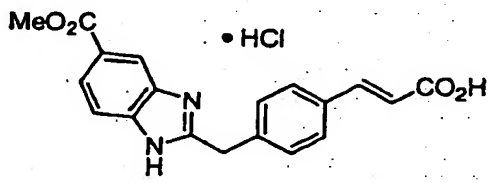
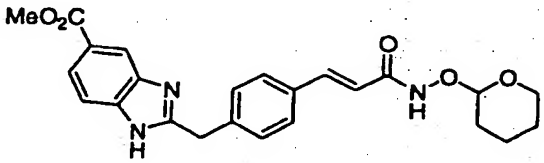
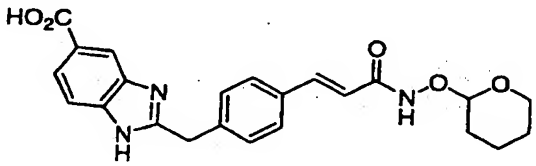
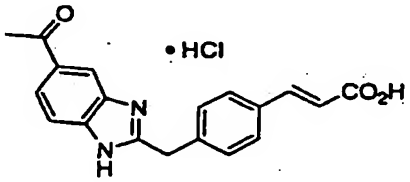
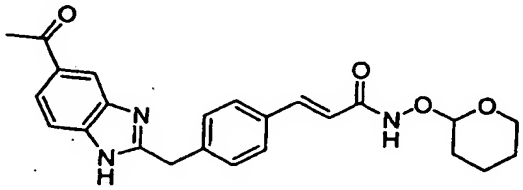
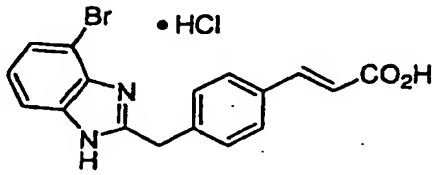
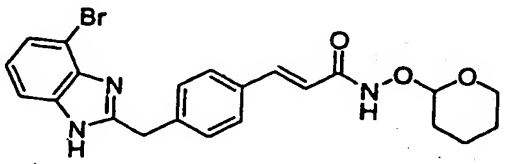
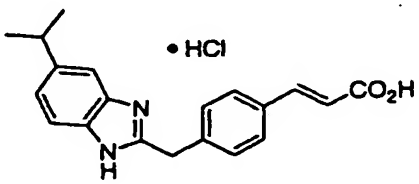
Compound (49)	Compound (50)
	
Compound (51)	Compound (52)
	
Compound (53)	Compound (54)
	
Compound (55)	Compound (56)
	

Table 2-8

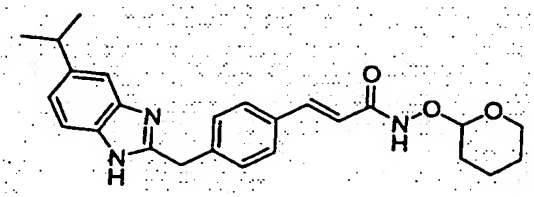
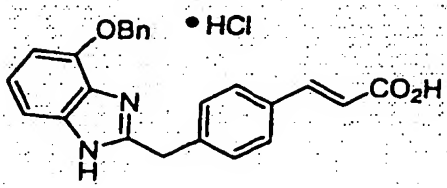
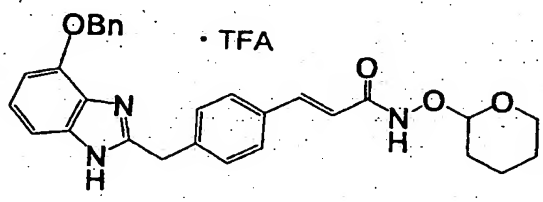
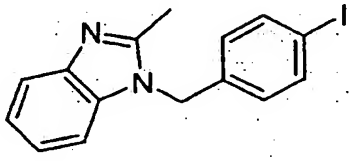
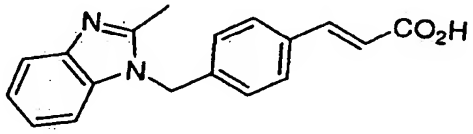
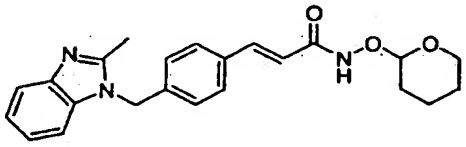
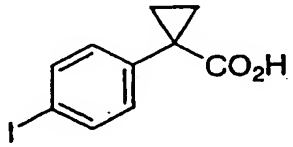
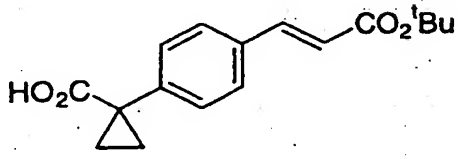
Compound (57)	Compound (58)
	
Compound (59)	**Compound (60)**
	
Compound (61)	**Compound (62)**
	
Compound (63)	**Compound (64)**
	

Table 2-9

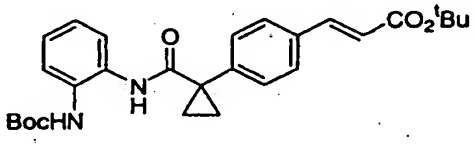
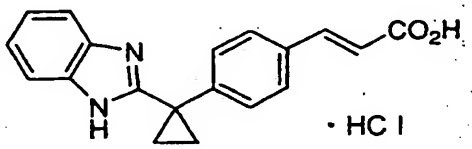
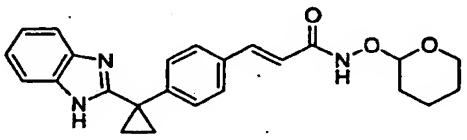
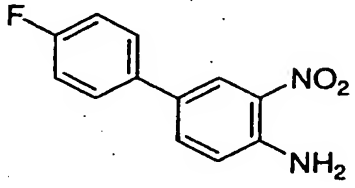
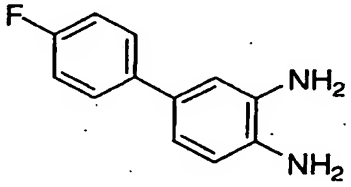
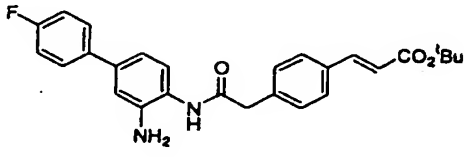
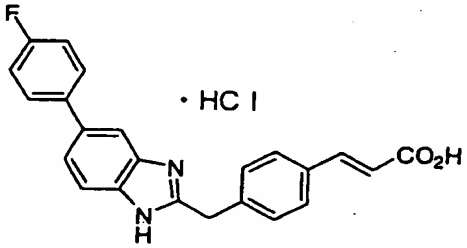
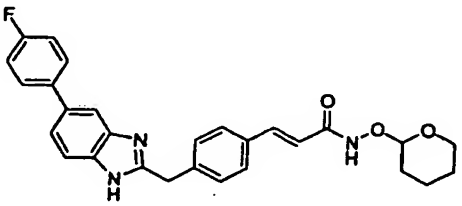
Compound (65)	Compound (66)
	
Compound (67)	**Compound (68)**
	
Compound (69)	**Compound (70)**
	
Compound (71)	**Compound (72)**
	

Table 2-10

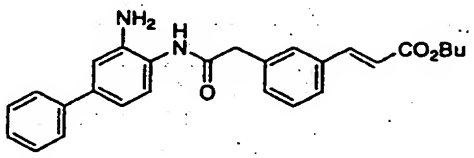
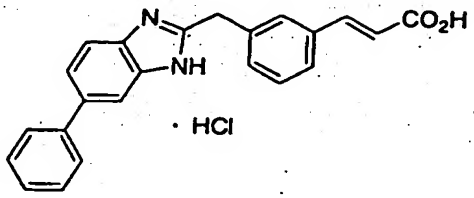
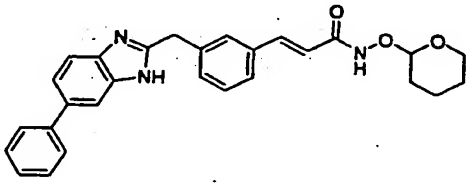
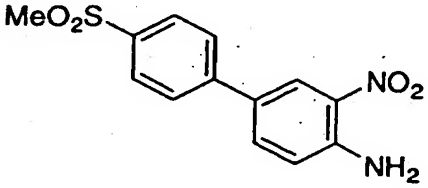
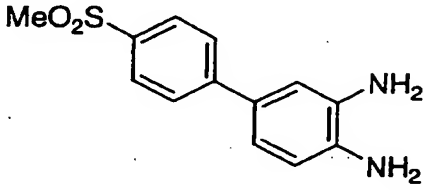
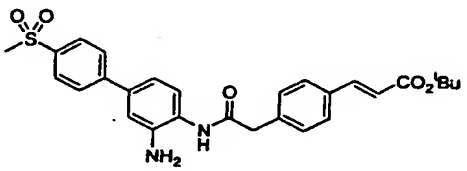
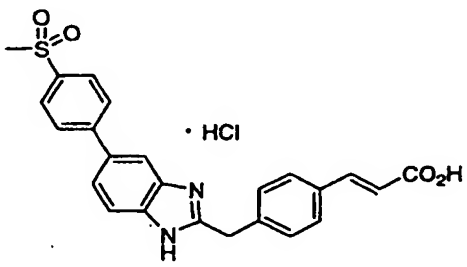
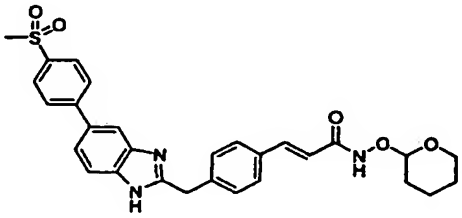
Compound (73)	Compound (74)
	
Compound (75)	**Compound (76)**
	
Compound (77)	**Compound (78)**
	
Compound (79)	**Compound (80)**
	

Table 2-11

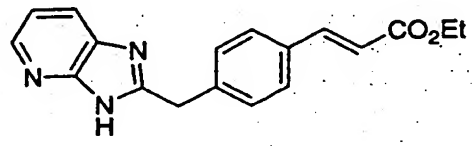
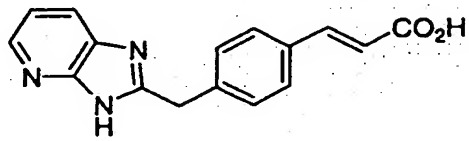
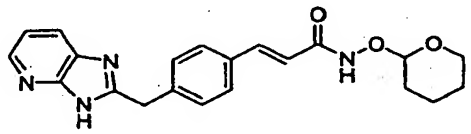
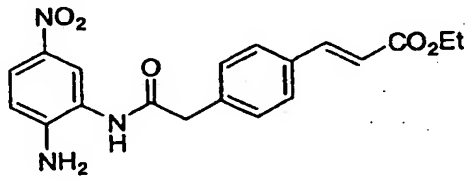
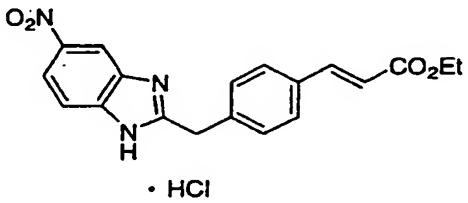
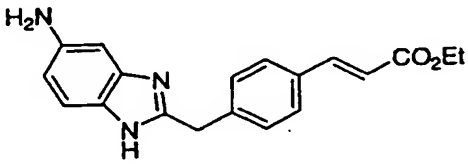
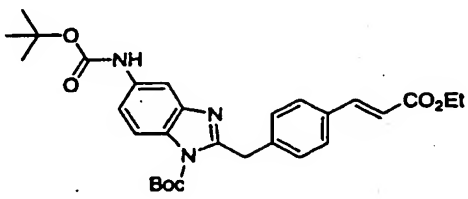
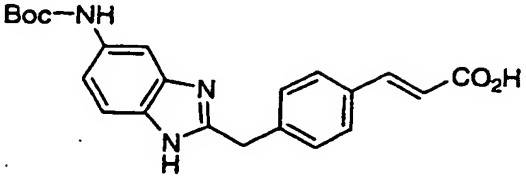
Compound (81)	Compound (82)
	
Compound (83)	**Compound (84)**
	
Compound (85)	**Compound (86)**
	
Compound (87)	**Compound (88)**
	

Table 2-12

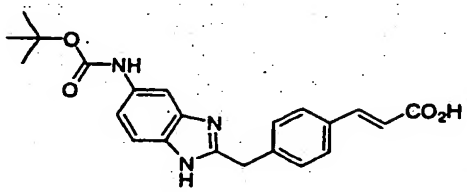
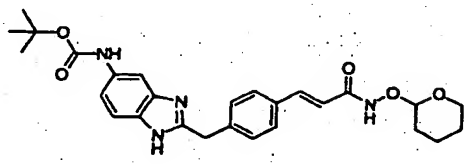
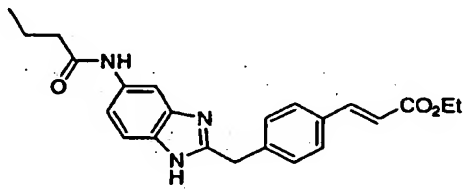
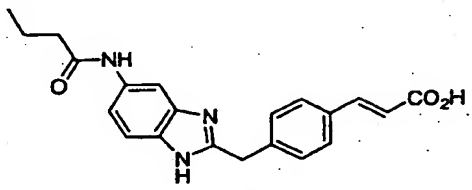
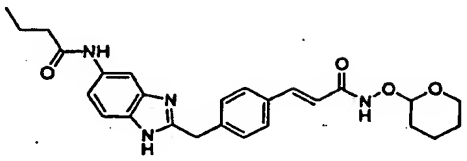
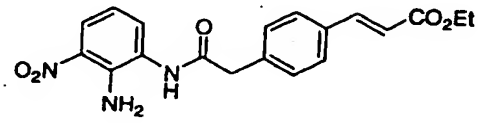
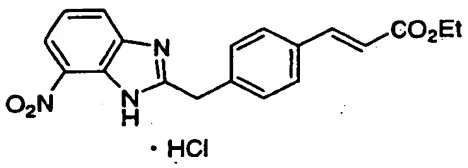
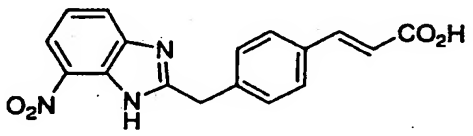
Compound (89)	Compound (90)
	
Compound (91)	**Compound (92)**
	
Compound (93)	**Compound (94)**
	
Compound (95)	**Compound (96)**
	

Table 2-13

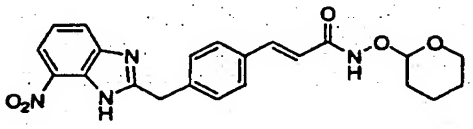
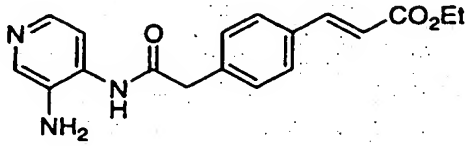
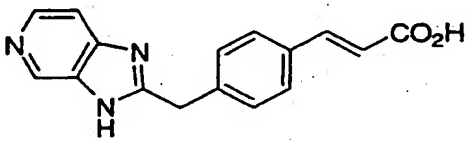
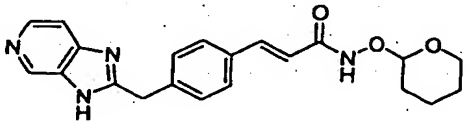
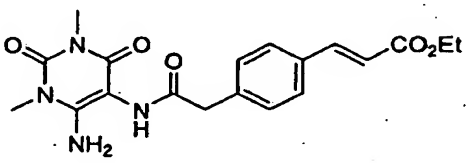
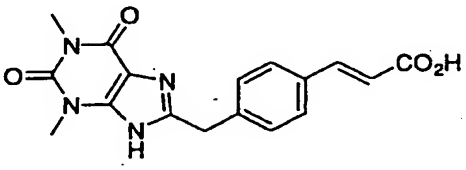
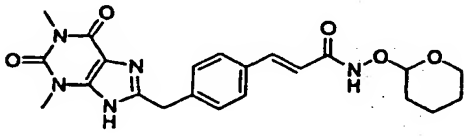
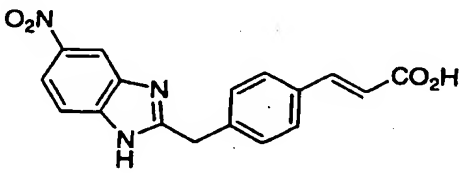
Compound (97)	Compound (98)
	
Compound (99)	**Compound (100)**
	
Compound (101)	**Compound (102)**
	
Compound (103)	**Compound (104)**
	

Table 2-14

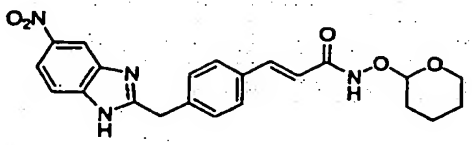
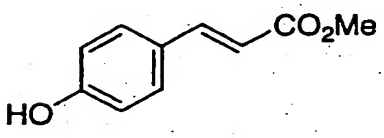
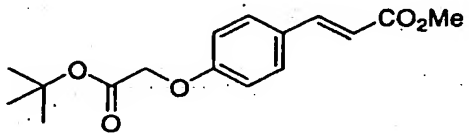
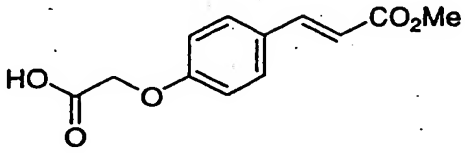
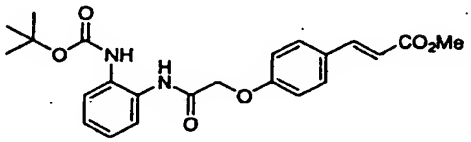
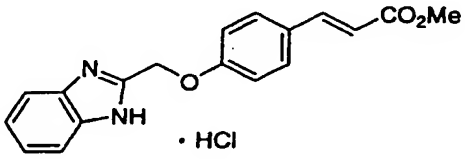
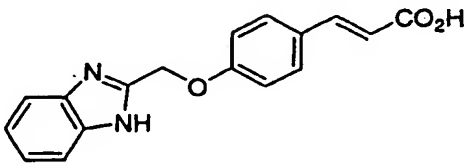
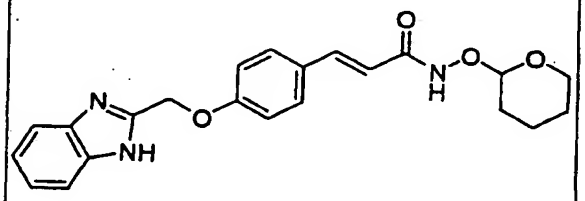
Compound (105)	Compound (106)
	
Compound (107)	**Compound (108)**
	
Compound (109)	**Compound (110)**
	
Compound (111)	**Compound (112)**
	

Table 2-15

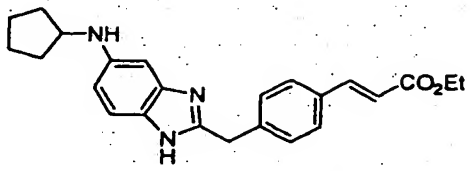
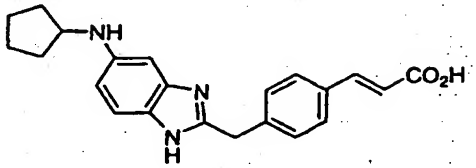
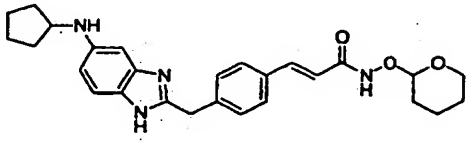
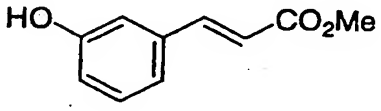
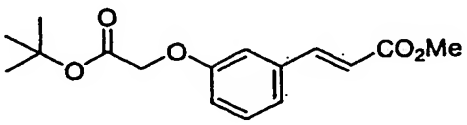
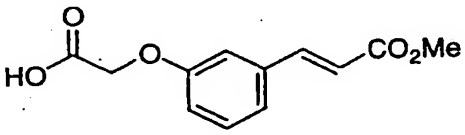
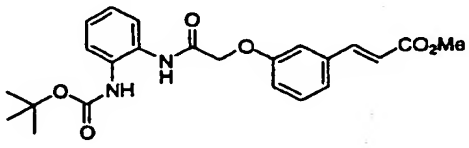
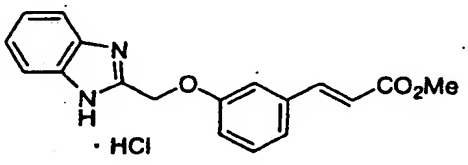
Compound (113)	Compound (114)
	
Compound (115)	**Compound (116)**
	
Compound (117)	**Compound (118)**
	
Compound (119)	**Compound (120)**
	

Table 2-16

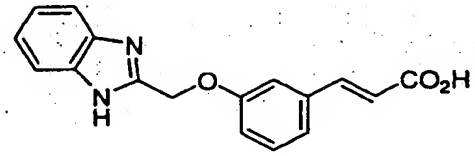
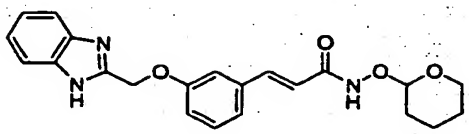
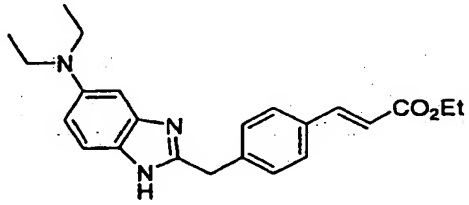
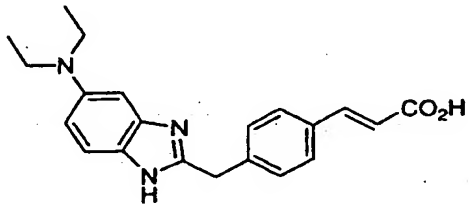
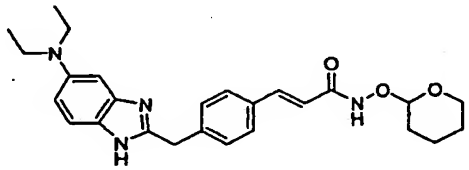
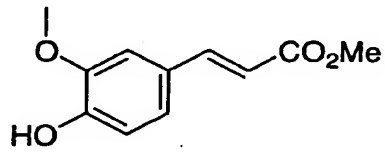
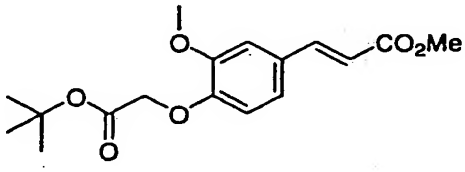
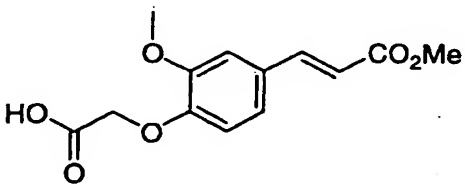
Compound (121)	Compound (122)
	
Compound (123)	**Compound (124)**
	
Compound (125)	**Compound (126)**
	
Compound (127)	**Compound (128)**
	

Table 2-17

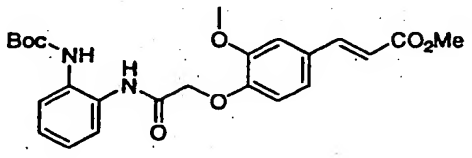
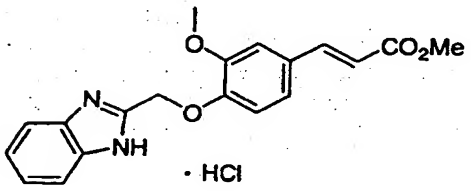
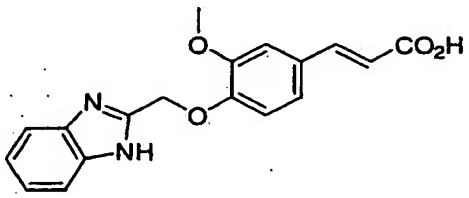
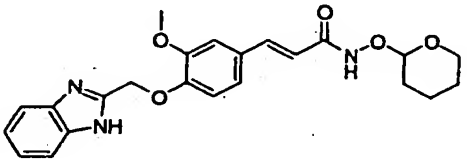
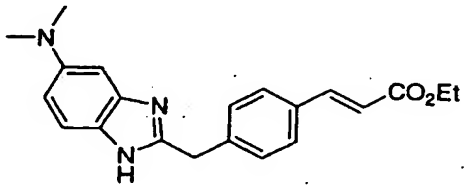
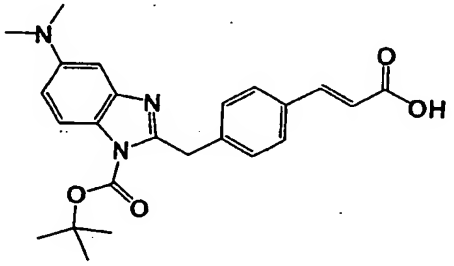
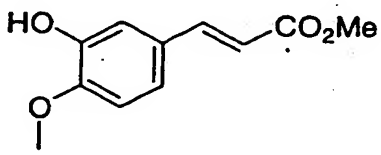
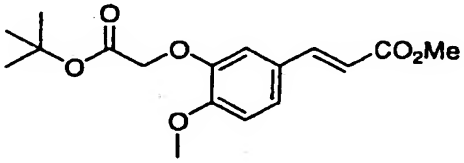
Compound (129)	Compound (130)
	
Compound (131)	**Compound (132)**
	
Compound (133)	**Compound (134)**
	
Compound (135)	**Compound (136)**
	

Table 2-18

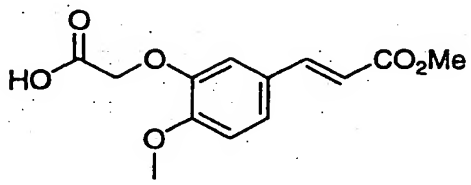
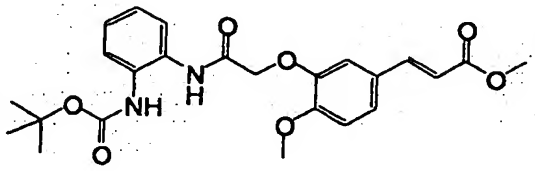
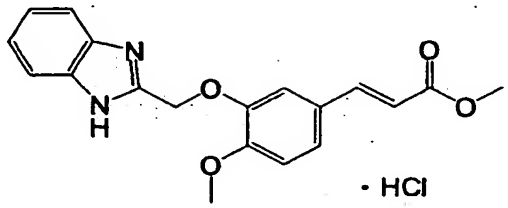
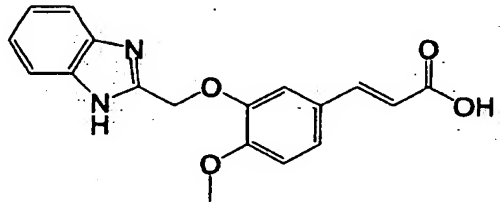
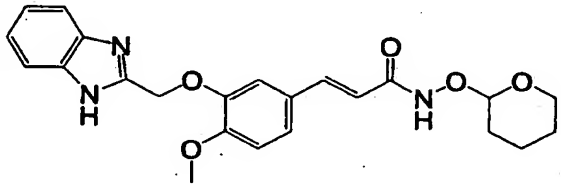
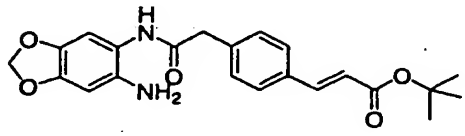
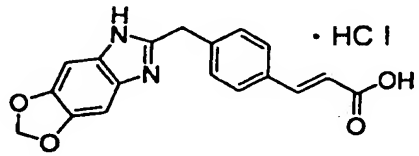
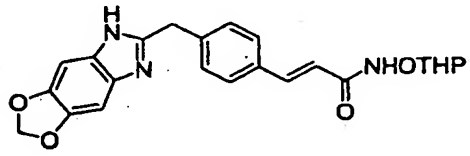
Compound (137)	Compound (138)
	
Compound (139)	**Compound (140)**
	
Compound (141)	**Compound (142)**
	
Compound (143)	**Compound (144)**
	

Table 2-19

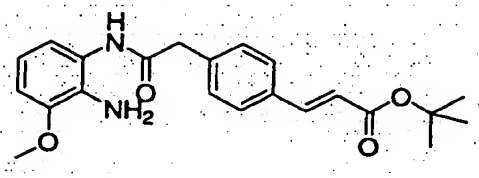
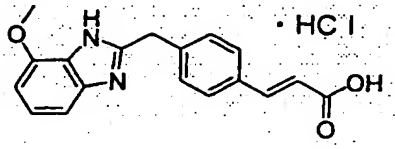
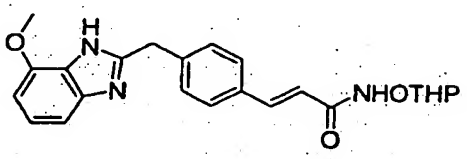
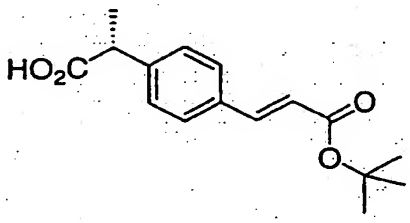
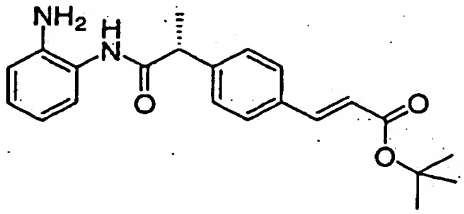
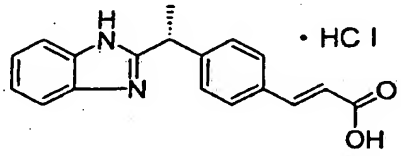
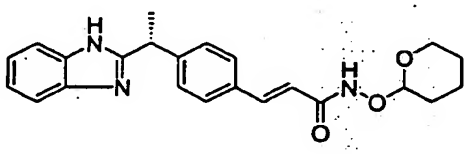
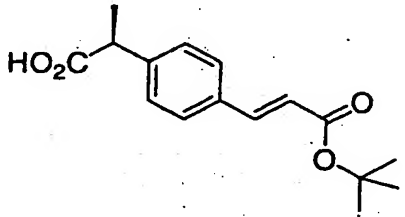
Compound (145)	Compound (146)
	
Compound (147)	**Compound (148)**
	
Compound (149)	**Compound (150)**
	
Compound (151)	**Compound (152)**
	

Table 2-20

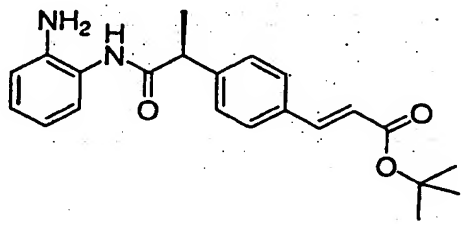
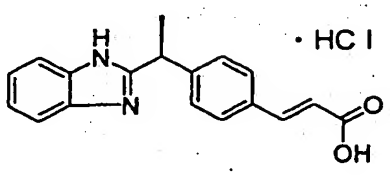
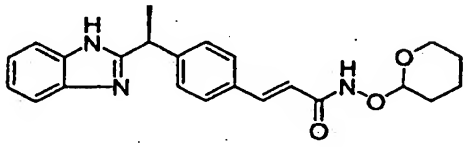
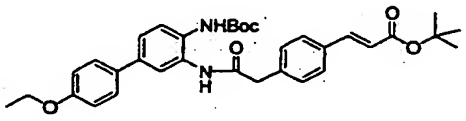
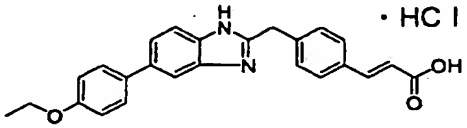
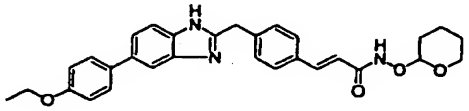
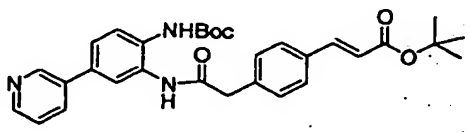
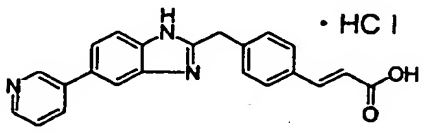
Compound (153)	Compound (154)
	
Compound (155)	**Compound (156)**
	
Compound (157)	**Compound (158)**
	
Compound (159)	**Compound (160)**
	

Table 2-21

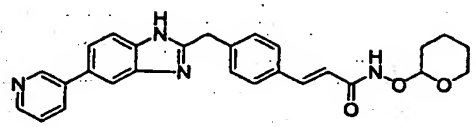
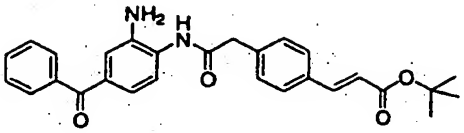
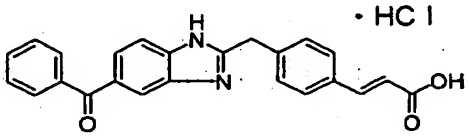
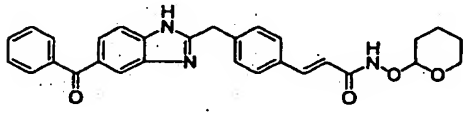
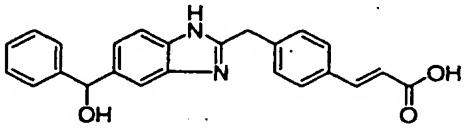
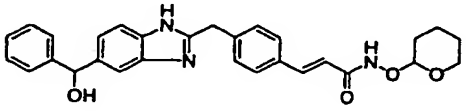
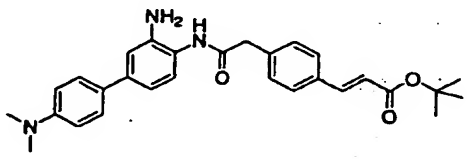
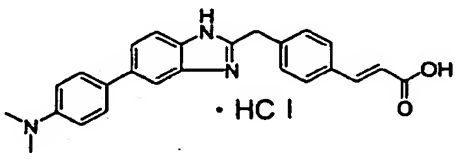
Compound (161)	Compound (162)
	
Compound (163)	**Compound (164)**
	
Compound (165)	**Compound (166)**
	
Compound (167)	**Compound (168)**
	

Table 2-22

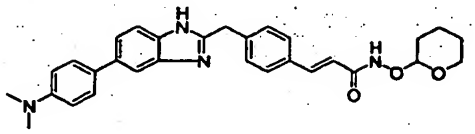
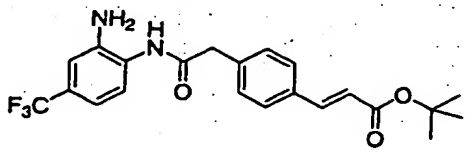
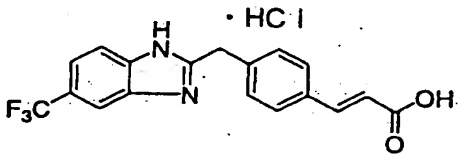
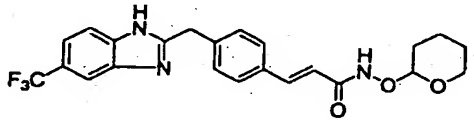
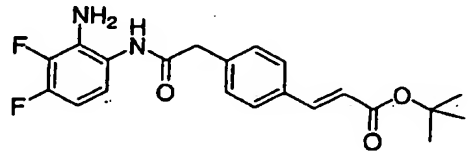
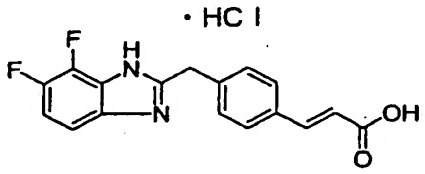
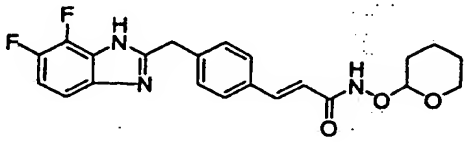
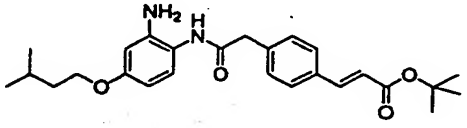
Compound (169)	Compound (170)
	
Compound (171)	**Compound (172)**
	
Compound (173)	**Compound (174)**
	
Compound (175)	**Compound (176)**
	

Table 2-23

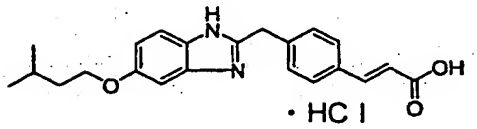
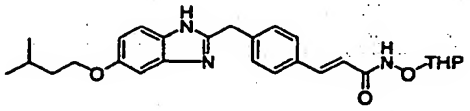
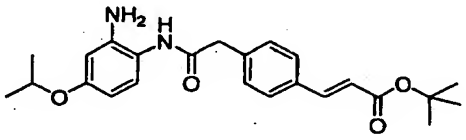
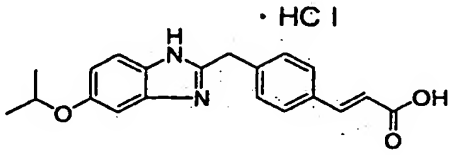
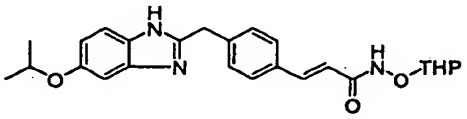
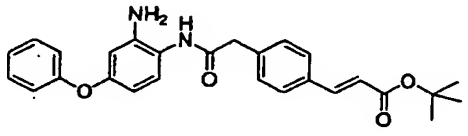
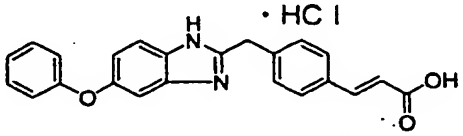
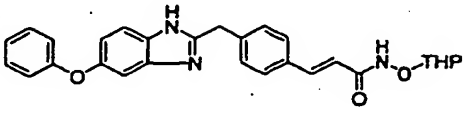
Compound (177)	Compound (178)
	
Compound (179)	**Compound (180)**
	
Compound (181)	**Compound (182)**
	
Compound (183)	**Compound (184)**
	

Table 2-24

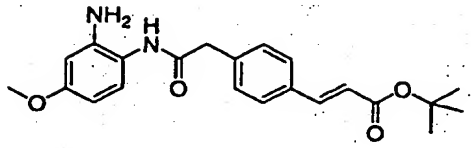
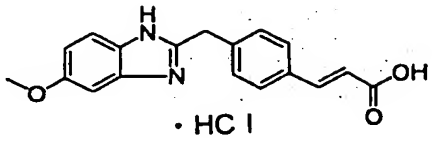
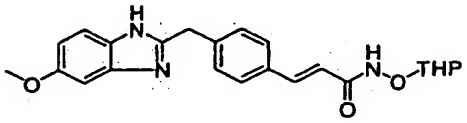
Compound (185)	Compound (186)
	
Compound (187)	
	

Table 3

Table 3-1

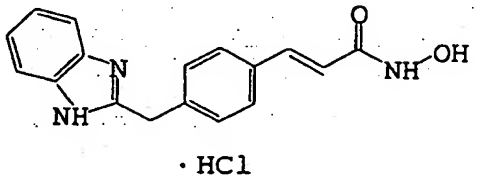
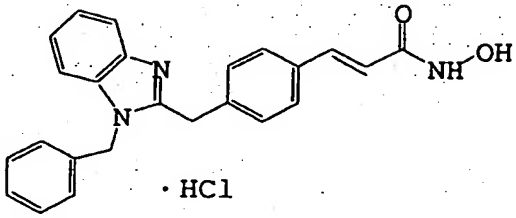
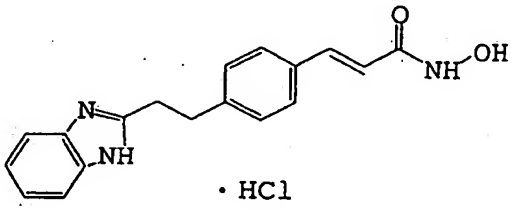
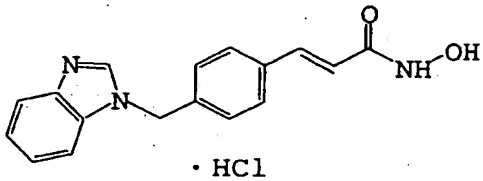
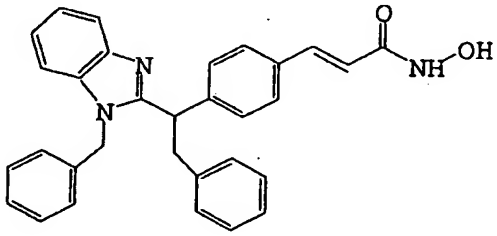
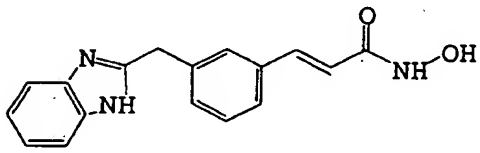
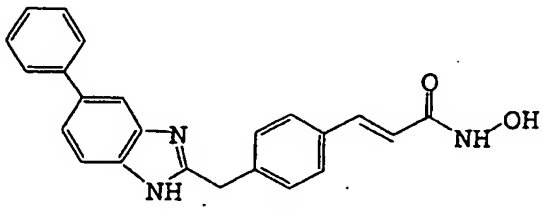
Compound E1	Compound E2
 · HCl	 · HCl
Compound E3	**Compound E4**
 · HCl	 · HCl
Compound E5	**Compound E6**
	 · HCl
Compound E7	
 · HCl	

Table 3-2

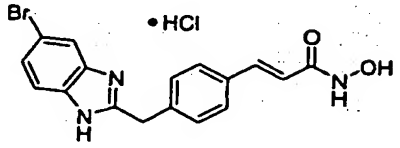
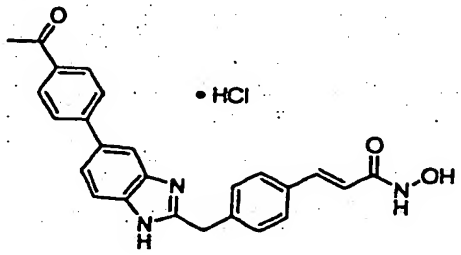
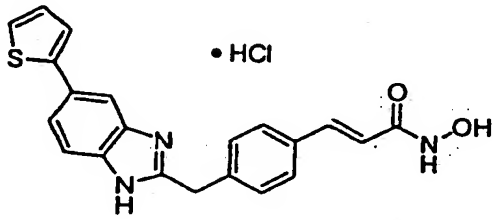
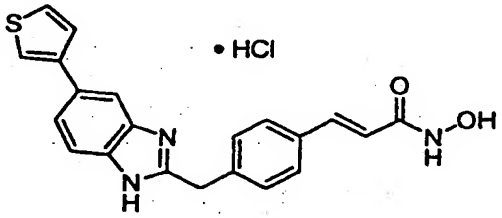
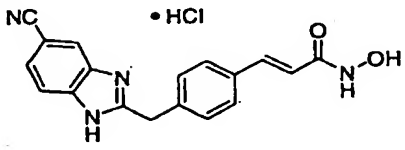
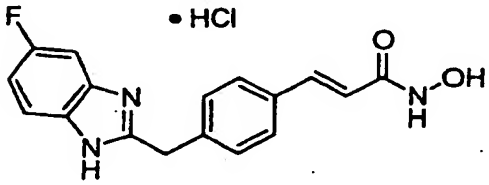
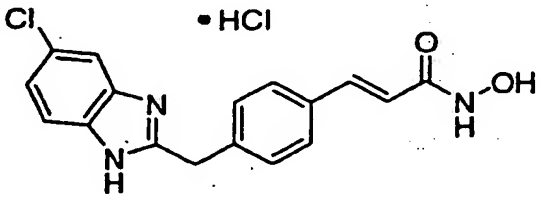
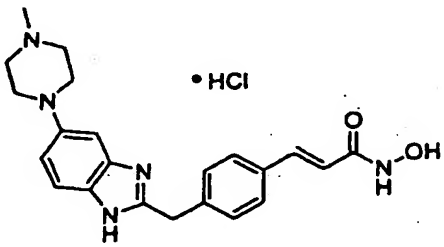
Compound E8	Compound E9
	
Compound E10	**Compound E11**
	
Compound E12	**Compound E13**
	
Compound E14	**Compound E15**
	

Table 3-3

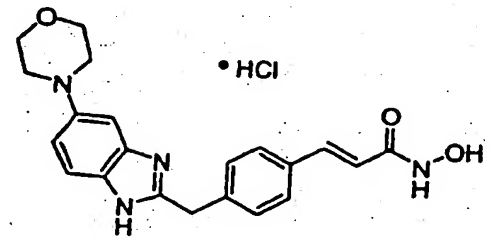
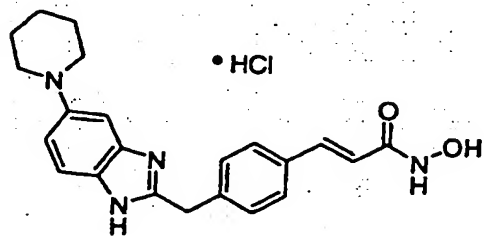
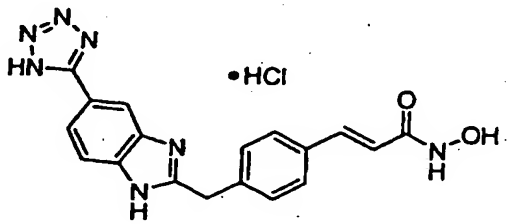
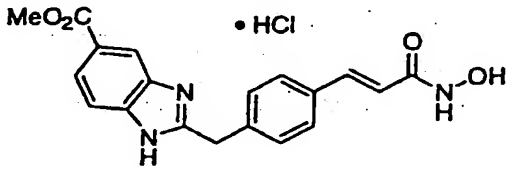
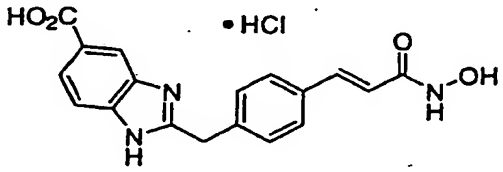
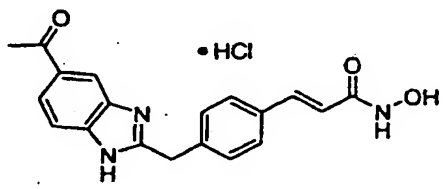
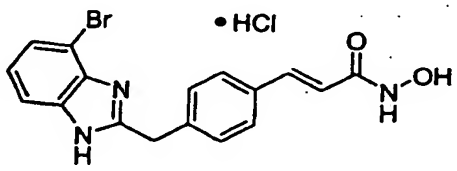
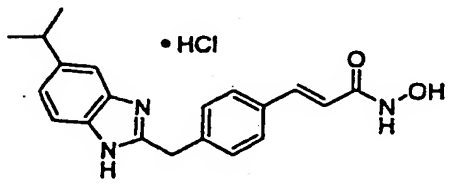
Compound E16	Compound E17
	
Compound E18	**Compound E19**
	
Compound E20	**Compound E21**
	
Compound E22	**Compound E23**
	

Table 3-4

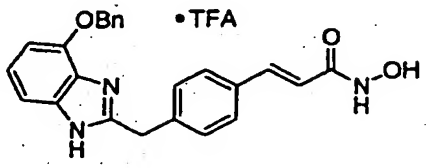
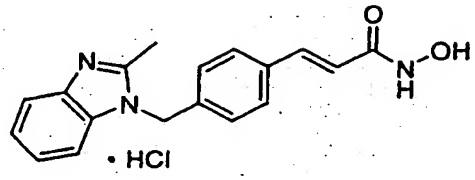
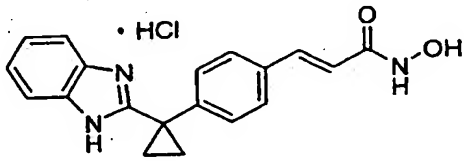
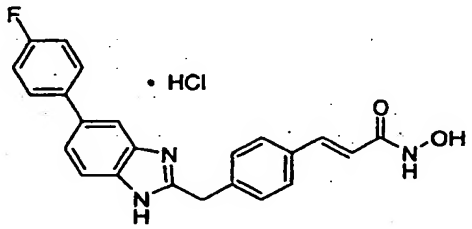
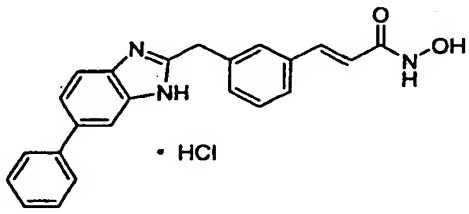
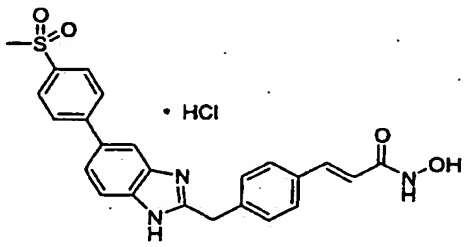
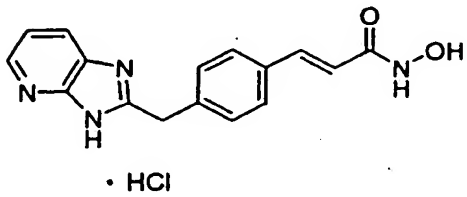
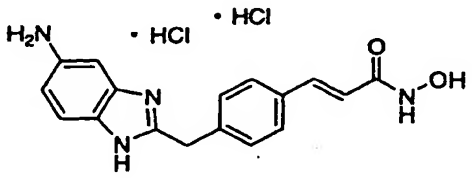
Compound E24	Compound E25
	
Compound E26	**Compound E27**
	
Compound E28	**Compound E29**
	
Compound E30	**Compound E31**
	

Table 3-5

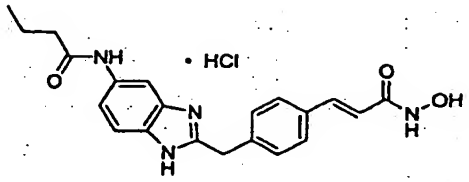
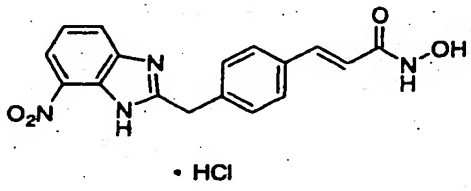
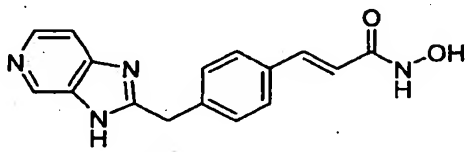
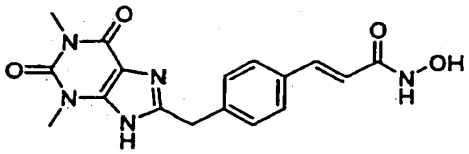
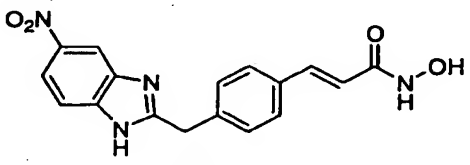
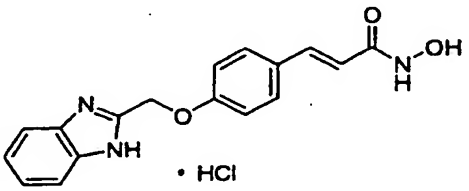
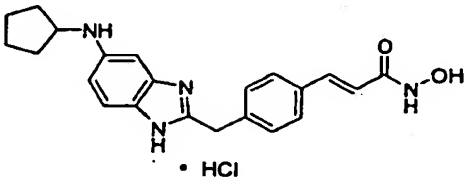
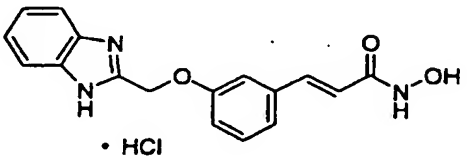
Compound E32	Compound E33
	
Compound E34	**Compound E35**
	
Compound E36	**Compound E37**
	
Compound E38	**Compound E39**
	

Table 3-6

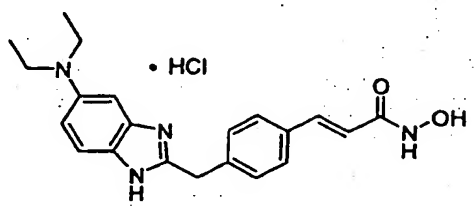
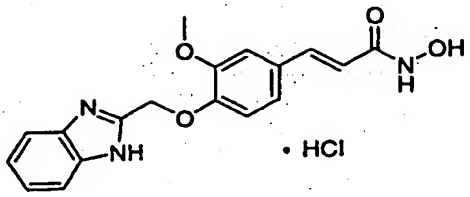
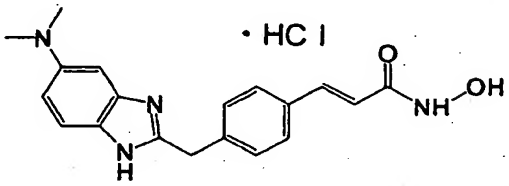
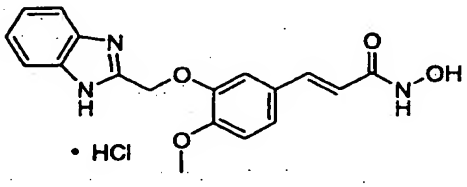
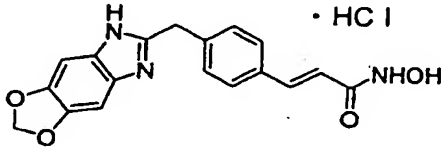
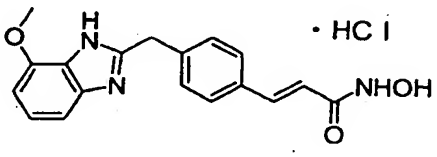
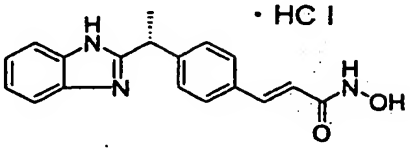
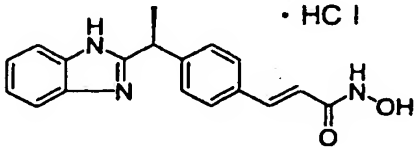
Compound E40	Compound E41
	
Compound E42	**Compound E43**
	
Compound E44	**Compound E45**
	
Compound E46	**Compound E47**
	

Table 3-7

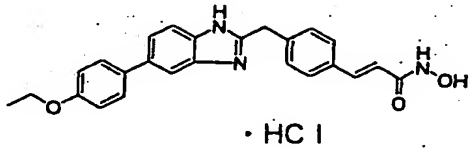
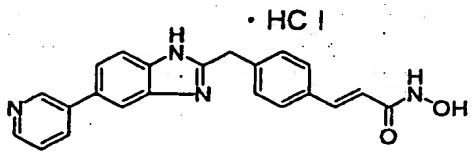
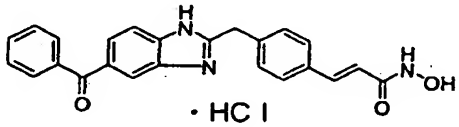
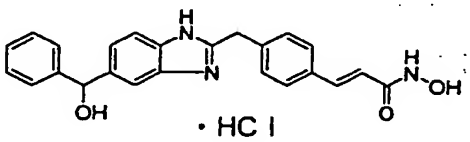
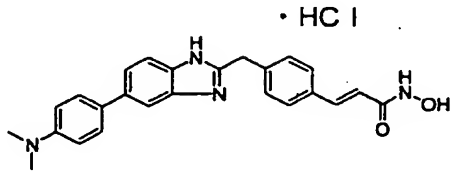
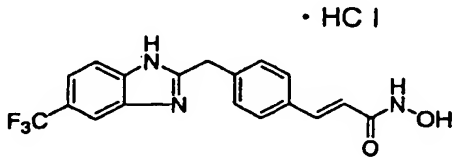
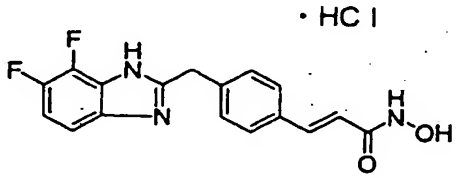
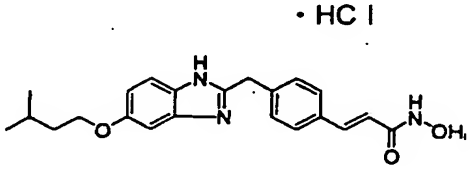
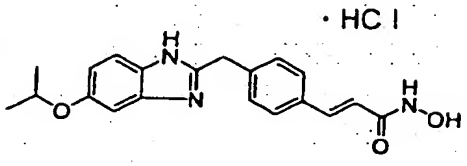
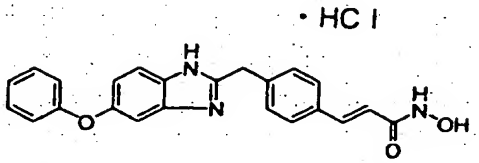
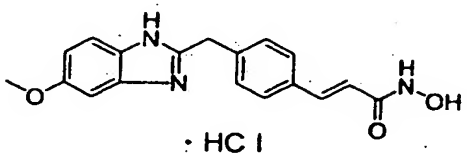
Compound E48	Compound E49
	
Compound E50	Compound E51
	
Compound E52	Compound E53
	
Compound E54	Compound E55
	

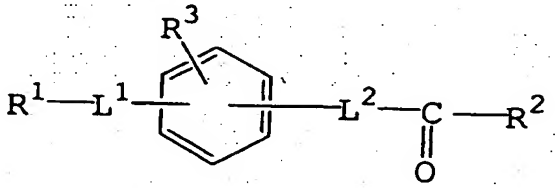
Table 3-8

Compound E56	Compound E57
	
Compound E58	
	

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

R^3 is hydrogen or a suitable substituent,

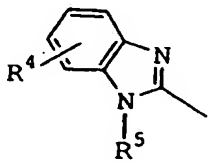
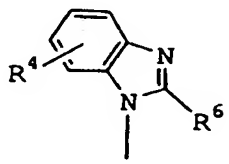
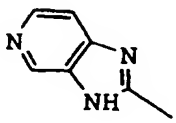
L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), wherein one or more methylene(s) may be replaced with suitable heteroatom(s), and

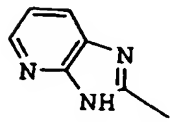
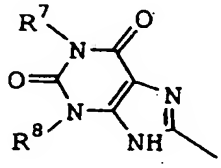
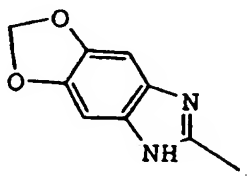
L^2 is lower alkenylene,

or a salt thereof.

2. The compound of claim 1, wherein

R^1 is N-containing condensed heterocyclic ring represented by the following formula:


,

,

,


,

or


wherein

R^4 is hydrogen or a group selected from the group consisting of

(1) lower alkyl,

(2) lower alkoxy,
(3) aryl optionally substituted with the substituent selected from the group consisting of halogen, lower alkanoyl, lower alkylsulfonyl, lower alkoxy and di(lower)alkylamino,
(4) lower alkanoyl,
(5) lower alkoxycarbonyl,
(6) arylcarbonyl,
(7) aryl(lower)alkoxy,
(8) amino optionally mono- or di-substitited with substituent(s) selected from the group consisting of lower alkyl, lower alkanoyl and cycloalkyl,
(9) halo(lower)alkyl,
(10) aryloxy,
(11) aryl(lower)alkyl optionally substituted with hydroxy,
(12) carboxyl,
(13) nitro,
(14) cyano,
(15) halogen,
(16) heteroaryl and
(17) non-aromatic heterocycle optionally substituted with lower alkyl,

R^5 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl, and

R^6, R^7 and R^8 are each hydrogen or lower alkyl,

R^2 is hydroxyamino,

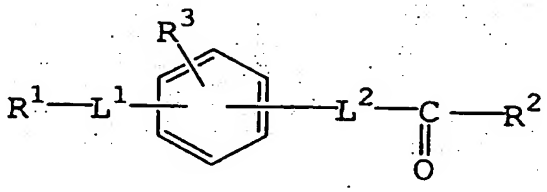
R^3 is hydrogen or lower alkoxy,

L^1 is $-(CH_2)_n-$ (wherein n is 1 or 2) optionally substituted with one or more substituent(s) selected from lower alkyl(s) and aryl(lower)alkyl, wherein two lower alkyls may form a ring, and wherein one methylene may be replaced with an oxygen atom, and

L^2 is vinylene,

or a salt thereof.

3. A histone deacetylase inhibitor comprising a compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

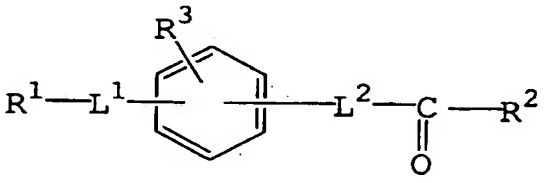
R^3 is hydrogen or a suitable substituent,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), wherein one or more methylene(s) may be replaced with suitable heteroatom(s), and

L^2 is lower alkenylene,

or a salt thereof.

4. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises a compound of the following formula (I) as an active ingredient:



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

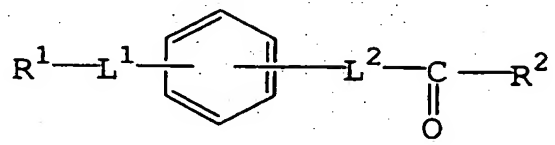
R^2 is hydroxyamino,

R^3 is hydrogen or a suitable substituent,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), wherein one or more methylene(s) may be replaced with suitable heteroatom(s),

and
L^2 is lower alkenylene,
or a salt thereof.

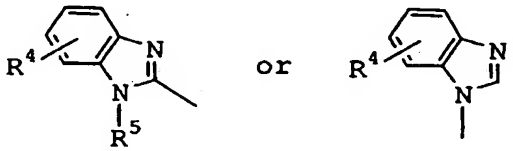
5. A compound having the following formula (I'):



(I')

wherein
R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),
R^2 is hydroxyamino,
L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and
L^2 is lower alkenylene,
or a salt thereof.

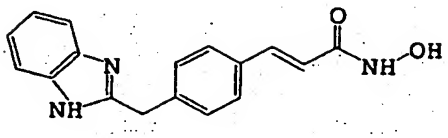
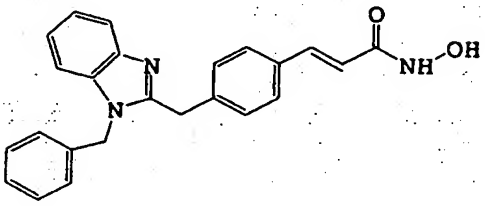
6. The compound of claim 5, wherein
R^1 is N-containing condensed heterocyclic ring represented by the following formula:



wherein
R^4 is hydrogen or a group selected from the group consisting of lower alkyl and aryl, and
R^5 is hydrogen or a group selected from the group consisting of lower alkyl and aryl(lower)alkyl,
R^2 is hydroxyamino,
L^1 is $-(CH_2)_n-$ (wherein n is 1 or 2) optionally substituted with aryl(lower)alkyl, and
L^2 is vinylene,
or a salt thereof.

7. The compound of claim 6, which is selected from the group

consisting of:


,

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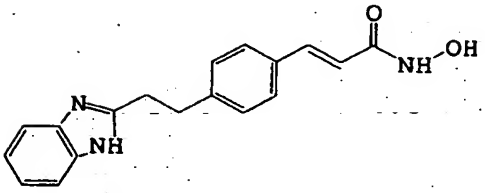
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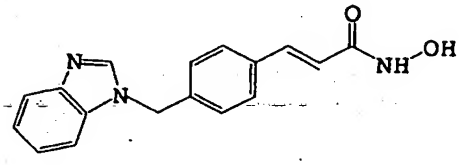
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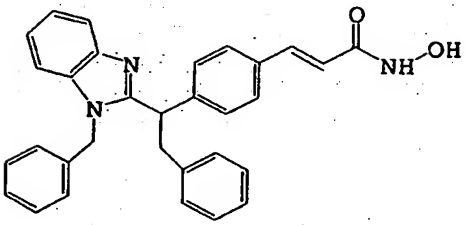
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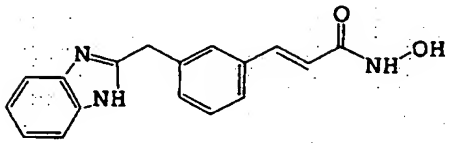
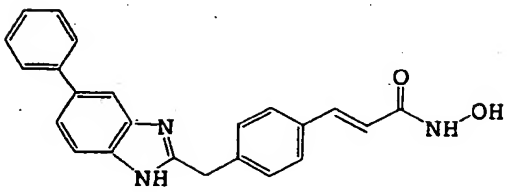
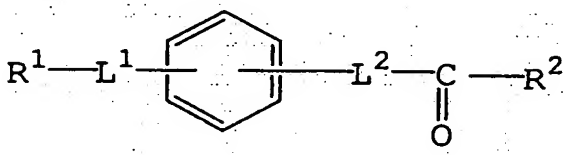

and


or a salt thereof.

5

8. A histone deacetylase inhibitor comprising a compound having the following formula (I'):



(I')

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

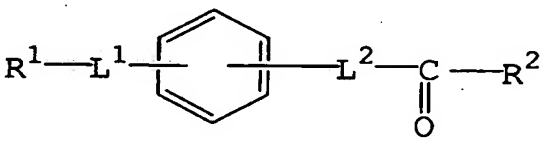
R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

or a salt thereof.

9. A pharmaceutical composition for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises a compound of the following formula (I') as an active ingredient:



(I')

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), and

L^2 is lower alkenylene,

or a salt thereof.

10. A pharmaceutical composition containing the compound of any of claims 1, 2 and 5 to 7 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

11. The compound of any of claims 1, 2 and 5 to 7 for use as a medicament.

12. A method for inhibiting histone deacetylase, comprising using the compound of claim 1 or 5.

13. Use of the compound of claim 1 or 5 for the manufacture of a medicament for inhibiting histone deacetylase.

14. A method for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors, which comprises administering an effective amount of the compound of claim 1 or 5 to a human being or an animal.

15. Use of the compound of claim 1 or 5 for the manufacture of a medicament for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

16. A commercial package comprising the pharmaceutical composition of claim 4 or 9 and a written matter associated therewith, the written matter stating that the pharmaceutical composition may or should be used for treating or preventing inflammatory disorders, diabetes, diabetic complications, homozygous thalassemia, fibrosis, cirrhosis, acute promyelocytic leukaemia (APL), organ transplant rejections, autoimmune diseases, protozoal infections or tumors.

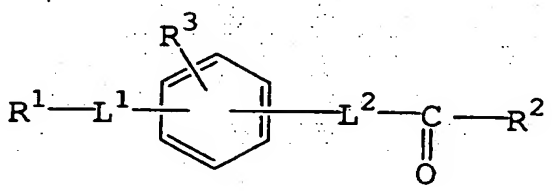
DATED this 6th day of October 2003

Fujisawa Pharmaceutical Co., Ltd.

By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

ABSTRACT

A compound having the following formula (I):



(I)

wherein

R^1 is N-containing condensed heterocyclic ring optionally substituted with one or more suitable substituent(s),

R^2 is hydroxyamino,

R^3 is hydrogen or a suitable substituent,

L^1 is $-(CH_2)_n-$ (wherein n is an integer of 0 to 6) optionally substituted with one or more suitable substituent(s), wherein one or more methylene(s) may be replaced with suitable heteroatom(s), and

L^2 is lower alkenylene,

or a salt thereof. The compound is useful as a histone deacetylase inhibitor.